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Νευροφυσιολογική διερεύνηση της συμμετοχής του προκινητικού φλοιού στις κινήσεις οφθαλμού και άνω άκρου

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Involvement of the premotor cortex in saccade and forelimb movement generation.

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SUMMARY

To study the response properties of cells that could participate in eye-hand coordination, we performed extracellular recordings from two macaque monkeys performing center-out saccades and forelimb pointing movements. We analyzed the phasic movement related discharges of neurons in the periarcuate cortex and separated them in seven distinct classes, based on the presence or absence of such phasic discharge before saccades, hand movements or combined eye-hand movements. We encountered 55 cells that fired before and during saccades and movements of the hand. Because they could encode an abstract form of the desired displacement vector without regard to the effector that would execute the movement, we refer to this class of cells as motor equivalence neurons (Meq). The onset of the phasic discharges of Meq cells was often correlated to both the onset of saccades and the onset of hand movements. Their on-directions were uniformly distributed without preference for ipsiversive or contraversive movements. In about half of the cells the preferred direction for saccades was the preferred direction for hand movements as well. In the remaining cells the difference was considerable (>90 deg). A three-layer neural network model that used Meq cells as its input layer showed that the lack of effector invariance in their discharge can help reduce the number of decoding errors when the network attempts to compute the correct movement metrics of the right effector.

We also found in the caudal bank of the arcuate sulcus cells that discharged in relation to saccades and not hand movements (S neurons). Unlike frontal eye field (FEF) presaccadic neurons, the on-directions of premotor S neurons had equal probability to be ipsiversive or contraversive. Since the onset of the phasic discharge S cells preceded that of FEF presaccadic neurons, they are unlikely to convey to their targets corollary discharges of signals arising in area 8. Apart from the familiar premotor cells discharging before forelimb movements (H cells), we encountered a small number of neurons that could function as logical gates: cells that discharged for saccades if they were not accompanied by hand movements (xS neurons), cells that discharged for hand movements if they were not accompanied by saccades (xH neurons), cells that discharged only for coordinated movements of the eyes and the hand (AND neurons)

and cells that discharged for saccades or movements of the hand but did not discharge for coordinated movements of both effectors (XOR neurons). Our findings are discussed in the context of sequences of decision processes stitching effector specific motor plans onto effector invariant movement primitives.

Finally, 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 frontal cortex 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 2mm behind the smooth pursuit area. Premotor sites elicited saccades with ipsiversive characteristic vectors. Premotor generated saccades had also lower peak velocities and flatter velocity profiles than FEF generated saccades.

ΠΕΡΙΛΗΨΗ

Για να μελετήσουμε τη νευρική δραστηριότητα που θα μπορούσε να συμμετάσχει στον συντονισμό σακκαδικών και κινήσεων άνω μέλους, διεξάγαμε εξωκυττάριες καταγραφές από τρία ημισφαίρια δύο πρωτεύοντων είδους Macaca mulata ενώ εκτελούσαν κινήσεις προς περιφερικούς στόχους με τους οφθαλμούς ή το άνω μέλος. Καταγράψαμε νευρώνες στην περιοχή εγγύς της τοξοειδούς αύλακας και αναλύσαμε την φασική και σχετιζόμενη με την εκτέλεση κινήσεων δραστηριότητα τους. Χωρίσαμε τους νευρώνες σε επτα διακριτές κατηγορίες με βάση την παρουσία ή απουσία σχετικής με κίνηση δραστηριότητας πριν την εκτέλεση κινήσεων άνω μέλους, σακκαδικών ή συνδιασμένων κινήσεων και με τους δύο φορείς. Βρήκαμε 55 κύτταρα με εκφόρτιση πριν και κατά την διάρκεια σακκαδικών και κινήσεων άνω μέλους. Τα κύτταρα αυτά θα μπορούσαν να κωδικοποιούν μια αφηρημένη μορφή του ανύσματος μετατόπισης, η οποία είναι ανεξάρτητη από τον φορέα που εκτελεί την κίνηση και, ως εκ τούτου, αναφερόμαστε σε αυτήν την τάξη νευρώνων με τον όρο κύτταρα κινητικής ισοδυναμίας (Motor equivalence κύτταρα ή Meq κύτταρα). Η έναρξη της φασικής δραστηριότητας των Meq κυττάρων συχνά συσχετιζόταν χρονικά με την έναρξη τόσο κινήσεων χεριού όσο και σακκαδικών. Οι προτιμώμενες κατευθύνσεις κίνησης των κυττάρων αυτών κατανέμονται ομοιόμορφα στον μοναδιαίο κύκλο, χωρίς να παρουσιάζεται υπερεκπροσώπηση ομόπλευρων ή ετερόπλευρων κινήσεων. Στα μισά περίπου κύτταρα η προτιμώμενη κατεύθυνση για σακκαδικές συνέπιπτε με την προτιμώμενη κατεύθυνση για κινήσεις άνω μέλους. Στα υπόλοιπα κύτταρα, η διαφορά ήταν αρκετά μεγάλη (>90 μοίρες). Ένα τεχνητό νευρωνικό δίκτυο με τρεις στοιβάδες και είσοδο την δραστηριότητα των Meq κυττάρων έδειξε ότι η παρουσία αναντιστοιχίας μεταξύ των πεδίων διαφορετικών φορέων κίνησης μπορεί να βοηθήσει στην μείωση των λαθών στην αποκωδικοποίηση όταν το δίκτυο επιχειρεί να υπολογίσει το σωστό άνυσμα μετατόπισης με τον σωστό φορέα. Στην οπίσθια όχθη της τοξοειδούς αύλακας βρήκαμε επίσης κύτταρα με δραστηριότητα σχετική με σακκαδικές αλλά όχι με κινήσεις χεριού (κύτταρα S). Σε αντίθεση με τους νευρώνες των πρόσθιων οφθαλμικών πεδίων, οι προτιμώμενες κατευθύνσεις αυτών των κυττάρων είναι εξίσου πιθανό να είναι είτε ομοπλευρές ή ετερόπλευρες. Η έναρξη της φασικής δραστηριότητας των S κυττάρων προηγείται αυτής των νευρώνων των πρόσθιων

οφθαλμικών πεδίων και συνεπώς είναι απίθανο η δραστηριότητά τους να μεταφέρει σήματα-αντίγραφα της δραστηριότητας της περιοχής 8. Πέρα απο τους γνωστούς νευρώνες του προκινητικού με δραστηριότητα σχετική με κινήσεις χεριού («Η κύτταρα» της μελέτης μας), βρήκαμε και ένα μικρό αριθμό κυττάρων που θα μπορούσαν να λειτουργούν ως λογικές πύλες: κύτταρα που είχαν δραστηριότητα για σακκαδικές μόνο όταν δεν συνοδεύονταν από κινήσεις χεριού (xS νευρώνες), κύτταρα που είχαν δραστηριότητα για κινήσεις χεριού μόνο όταν δεν συνοδεύονταν από σακκαδικές (xH νευρώνες), κύτταρα που είχαν δραστηριότητα για συντονισμένες κινήσεις και των δύο φορέων αλλα όχι για κινήσεις χεριού ή για σακκαδικές (AND νευρώνες) και, τέλος, κύτταρα που είχαν δραστηριότητα για κινήσεις χεριού ή για σακκαδικές, αλλά όχι για συντονισμένες κινήσεις και των δύο φορέων (XOR νευρώνες). Τα ευρήματα αυτά συζητώνται στο πλαίσιο μιας σειράς διεργασιών λήψης αποφάσεων οι οποίες διασυνδέουν ειδικά για φορείς κινητικά πλάνα με κινητικά θεμελιακά στοιχεία που είναι ανεξάρτητα από τον φορέα της κίνησης.

Τελος, προκειμένου να εξετάσουμε την υπόθεση ότι ο προκινητικός φλοιός εντός και πίσω από την οπίσθια όχθη της τοξοειδούς αύλακας μπορεί να παράγει σακκαδικές, διεγείραμε με ηλεκτρικό ερεθισμό τον μετωπιαίο λοβό εγγύς της τοξοειδούς αύλακας. Εκλύθηκαν σακκαδικες από περιοχές του προκινήτικου που βρισκονται σε ανατομική συνέχεια με τα πρόσθια οφθαλμικά πεδία και επεκτείνονταν εως 2 χιλιοστά πίσω από την περιοχή αναπαράστασης των οφθαλμικών κινήσεων ομαλής παρακολούθησης. Οι παραγόμενες από τον προκινητικό σακκαδικές είχαν ομόπλευρα χαρακτηριστικά ανύσματα. Επίσης παρουσίαζαν χαμηλότερες μέγιστες ταχύτητες και πιο επίπεδα προφίλ ταχύτητας σε σχέση με τις κινήσεις που παράγονται απο διέγερση των πρόσθιων οφθαλμικών πεδίων.

INTRODUCTION

During free viewing the salience of visual features dominates gaze behavior (Yarbus, 1967). On the other hand, during purposeful tasks gaze behavior is entangled with arm action (Ballard et al., 1992). In fact, everyday activities depend on very well coordinated sequences of eye and hand movements (Land and Hayhoe, 2001). Hand movements place important constraints on the target of eye movements and the duration of fixations during visually guided reaches and grasps (Johansson et al., 2001) as well as during natural movements of everyday activities such as tea preparation (Land et al., 1999). Eye movements usually precede hand movements by tens of milliseconds and the close spatiotemporal coupling of hand and eye movements—within a few centimeters and milliseconds—is required for decent performance in demanding motor tasks, as Land et al. (2000) showed in cricket batters of varied skill.

Psychophysical evidence for shared representations of hand and eye movements

The cooperation of the saccadic and hand movement systems is underscored by the fact that they are affected in a remarkably similar manner by specific behavioral manipulations. For example, the insertion of a gap between the disappearance of the central fixation point and the appearance of a peripheral target (gap task) reduces the reaction time both for saccades and hand movements (Rogal et al., 1985; Sailer et al., 2000; Gribble et al., 2002). Movement towards a direction diametrically opposite to that of the visual target (anti-saccade/anti-reach task) results in longer reaction times for both effectors (Sailer et al., 2000). A moving background alters the perception of the motion of both saccadic and hand movement targets and affects eye and hand movements accordingly (Soechting et al., 2001). The presence of a distractor near the target causes saccades to often land between the target and the distractor. This spatial averaging "global effect" (Findlay, 1982; Kapoula, 1985) has been shown to affect hand movements as well. Using a distractor less eccentric than the target, leads to smaller movements of both the eyes and the hand. Conversely,

using a distractor more eccentric than the target, leads to bigger movements of both the eyes and the hand (Sailer et al., 2002a; Sailer et al., 2002b).

The notion that movements of the eyes and hand are coupled (at least temporally) is supported by one of the symptoms of the parietal syndrome, directional hypokinesia, which leads to an increase of reaction times of both hand movements (Faugier-Grimaud et al., 1985; Mattingley et al., 1994) and saccades (Girotti et al., 1983) to contralateral targets. The same is true in the monkey where LIP lesions delay the onset of both the saccadic and the reaching components of coordinated eye-hand movements (Yttri et al., 2013). Additionally, cerebellar ataxia, an autosomal dominant disease affecting voltage gated Ca^{++} channels, produces strikingly similar behaviors for eye and hand movements regarding both the time course of the movements and the spatial pattern of the trajectories (Engel et al., 2002). Spatial coupling of saccade and reaching movements is also suggested by a case of "magnetic misreaching" displayed by a patient who suffered from bilateral parietal lobe atrophy and was unable to avoid reaching to the place she was fixating (Carey, 2000).

In the case of magnetic misreaching, the patient's gazing affected dramatically arm behavior. Interestingly, in normal subjects too, accompanying saccades do alter hand movement parameters. Execution of saccades alongside with arm movements towards the same visual target results in arm movements of larger amplitude (van Donkelaar et al., 2000). This effect is more pronounced for saccades of larger amplitude (the eye and the hand capture the same target but start from different initial positions; the initial eye position is further from that of the hand) and is retained even when that arm is not visible (Van Donkelaar, 1997; 1998). Initial hand acceleration is larger when hand and eye movement onsets are closer temporally (Van Donkelaar, 1998). The gradual adaptation of saccades in the double step task (in which targets are displaced to shorter or larger amplitudes right after the onset of the saccades) also seems to transfer to hand movements when they are executed in coordination with those saccades (Bekkering et al., 1995). These authors asked subjects to look at and point (with the help of a hand held device) to a target appearing on a cathode ray tube. Near the onset of the saccade, the target jumped 2 degrees back, towards the fixation point. Initially the subjects overshot the target and needed to execute a second, corrective saccade, to acquire it. After a few trials the saccade was adapted and its smaller size drove the eyes directly to the final position of the target. The hand movement was also adapted showing similarly shortened amplitudes

The interplay of the two systems is bidirectional, as saccadic parameters are also affected by accompanying hand movements. Saccades become faster (Snyder

et al., 2002) and more accurate if they are executed along with hand movements (Lünenburger et al., 2000). Saccadic reaction times were shorter when the hand movement was towards the same target, but prolonged when the hand movement was in the opposite direction (Lünenburger et al., 2000). In addition, the magnitude of force required for arm movement in conditions where an external load exerts either resistance or facilitation, influences parameters of saccades even before the hand movements were executed (van Donkelaar et al., 2004).

Given these observations it is reasonable to ask if hand and eyes in these conditions are driven by a common command or by separate and parallel processes (Bekkering et al., 1994). The notion that a single command signal might drive more than one movement effector is closely related to the idea of motor equivalence introduced by Lashley (1930) and refined by Nikolai Bernstein (1967) which suggests that the movement parameters are encoded by the brain in an abstract way that is not tied to specific muscle actions and, therefore, is independent of the effector employed. The most cited example of motor equivalence is handwriting, which even though it is learned to be executed with one's dominant hand, it can be performed with the foot and the major elements of one's writing style are retained. (Wing, 2000). Bernstein's approach to motor equivalence addresses the problem of the redundant degrees of freedom in movement control. The human body contains 244 degrees of freedom and just the human hand has 27 degrees of freedom (Zatsiorsky and Prilutsky, 2012). This implies that movement control also lies in a space of accordingly high dimensionality, rendering it computationally demanding. On the other hand, only 3 degrees of freedom are needed to specify the locations of the target and the end effector, assuming that the shape of the limb is irrelevant. Bernstein suggested that the brain simplifies the movement control by using muscle synergies, which in turn are controlled in fewer dimensions. Motor synergies entail the co-ordinated coactivation of muscles by a single command (Latash et al., 2007).

To answer whether eyes and hand are engaged by such a single command, one straightforward approach is to evaluate the correlation of the reaction times of saccades versus those of hand movements. Higher correlation coefficients would support the argument for a common signal driving both movements, while lower coefficients would hint that that the command signals driving eyes and hand are more likely independent. These have been variously reported as very low or insignificant (Bekkering et al, 1994 ; Mather and Fisk, 1985), poor ($r<0.4$; Biguer et al., 1982; Frens and Erkelens, 1991), middling (≈0.5; Prablanc et al., 1979; Gielen et al., 1984; Fischer and Rogal, 1986; Sailer et al., 2000; Suzuki et al., 2008) or high (>0.6; Herman

et al., 1981; Fischer and Rogal, 1986; Frens and Erkelens, 1991; Suzuki et al., 2008; Yttri et al., 2013). This divergence of reported correlations leads different authors to varied conclusions. However, even low correlations often are highly significant, as in the case of the study by Biguer et al. (1982). They measured the latency of eye, head and hand movements towards targets and although correlation coefficients were below 0.5, they were significant at the 0.001 level.

There are also hints that the two systems use common spatial representations. Nemire and Bridgeman (1987) asked subjects to use saccades and a hand held pointer to pursue targets with or without interferences. The interferences were interjected after the peripheral target went off and before the instruction to execute the eye and hand movements and consisted of long delays or the execution of multiple saccades towards intermediate targets. The interferences affected saccadic and manual responses in a similar and highly correlated way both between sessions and within each session and the authors interpreted this as evidence that the two systems share a single map of space. Sailer et al (2000) could not find any correlation of variable errors between saccades and hand movements when the subjects were asked to perform the movement in step, gap (that is when a brief pause is added between the disappearance of the fixation point and the appearance of the peripheral target), memory, scanning and anti-saccade/anti-reach (i.e, when both eyes and hand move in a direction diametrically opposite to that of the target) tasks. They did find that movement onset times where correlated, especially for intentional tasks (memory, scanning, anti-saccade tasks) versus reflexive ones (gap, flashed, pro-saccade tasks). Studies of constant errors also point towards a common spatial representation of a common target for both effectors. For example, spatial errors of horizontal saccades of human subjects were larger for targets 20^{o} away than for targets 10^{o} away and they were larger for briefly presented targets than for persistent targets (Fisk and Goodale, 1985). The same was true of their reaching movements so that the correlation between the end point of eyes and forelimb was statistically significant ($t=3.3$, $p < 0.01$) albeit low ($r = 0.17$). In another study, Kattoulas et al. (2008) focused on the constant errors of saccades towards memorized targets and the reaching movements they accompany. The endpoints of saccades executed by monkeys towards the memorized location of visual targets land above the targets, displaying an upward shift irrespective of target location (Gnadt et al., 1991; Stanford and Sparks, 1994; White et al., 1994). Arm-pointing movements, on the other hand, display a very different pattern of constant errors. Subjects tend to direct their movements away from cardinal and toward oblique directions (Smyrnis et al., 2000; Smyrnis et al., 2007). Given these

two very different biases, it is reasonable to ask what pattern of errors would materialize when subjects are asked to both look and point towards memorized targets. To address this question, adult rhesus monkeys were trained to both reach and look towards targets in a center out memory task. Systematic saccade error was in this case found to co-vary with reaching error (Kattoulas et al., 2008). The percentage of the variance of saccadic errors accounted by reaching errors could be as high as 34% ($p<10^{-5}$). It might also be more meaningful to study the early part of the eye and pointing movements which rely on the initial displacement command rather than later on-line corrections operating for the hand. This is what Frens and Erkelens (1991) did in a study where subjects quickly fixated and pointed at unexpectedly presented eccentric targets. When a gap was introduced between extinction of a fixation point and target presentation, the error rate in the initial movement direction of saccade and hand movements increased to about 50%. Yet, saccade and hand movements were always made in the same direction, which again suggests that eye and hand can be guided by the same displacement command.

The premotor cortex and its role in movement generation

To resolve if a single common command could drive the eyes and hand, one could try to locate the neuronal discharge that represents it. The premotor cortex (Brodmann's area 6) is eminently deserving of such a search. When one signs one's name with the index finger or the toe, the region of the primary motor cortex activated depends on the effector performing the movement, whereas the same region of the premotor cortex is activated regardless of which effector is used (Rijntjes et al., 1999). The premotor cortex was recognized as distinct from the primary motor cortex (M1) in early cytoarchitectonic studies (Brodmann, 1905; Cambell, 1905) using the presence of numerous large layer five pyramidal cells as the distinguishing feature of M1 . Newer techniques provide additional tools to distinguish the premotor from the primary motor cortex. Thus, the premotor cortex can also be identified by the relative paucity of corticospinal neurons (Sessle and Wiesendanger, 1982), the lack of efferents to the magnocellular red nucleus(Catman-Berrevoets et al., 1979; Monakow et al., 1979), the presence of afferents from the posterior parietal cortex, the considerable higher stimulation threshold to produce evoked movements and the presence of neurons active during movement preparation (Godschalk et al., 1984; Wise, 1985). Dum & Strick's (2002) definition of the premotor cortex rests on the existence of direct

projections to the primary motor cortex and, therefore, emphasizes the hierarchical organization of the cortex.

Early inactivation studies by Fulton (Fulton, 1935), though crude, showed loss of skill in movement execution. Woolsey identified the supplementary motor cortex in the medial agranual cortex. He did not think, though, that the rest of the area 6 contributed to movements, as electrical stimulations did not produce movements and lesions extended to this area did not produce additional deficits. However their stimulations were made in anesthetized animals with barbiturates and their lesions were added to past ones in primary motor cortex and supplementary motor area (Woolsey, 1952; Travis, 1955). A role in generation of complex movements has been suggested as well. Jacobsen's (1934) lesions produced deficits in execution of complex movements. However, it's worth noting that their lesions also included the medially located supplementary motor areas. Also supportive of this view is the Graziano et al (2002) study, where complex and seemingly purposeful movements were produced by electrical microsimulations of the premotor cortex. In order to obtain those movements, the authors employed unusually prolonged stimulation trains (500 ms) of intensitiy ranging from 25 to 150 μA.

More established is the role of the premotor cortex in sensory guided movements, as it has been documented by numerous studies using diverse approaches. Roland et al (Roland et al., 1980) used ^{133}Xe injections to the internal carotid in 19 patients to evaluate the regional blood flow changes during various visually guided movements. They noted increased perfusion of the primary motor cortex, the premotor cortex—including both the supplementary motor area and the lateral convexity of the premotor cortex—the primary somatosensory cortex and the inferior and superior parietal regions. Moreover, the premotor cortex receives afferent inputs from visual areas (Pandya and Kuypers, 1969) and contains neurons responsive to visual (Rizzolatti et al., 1981), auditory (Graziano et al., 1999) or tactile stimuli (Graziano et al., 1997). Ablation of the premotor cortex itself produces deficits in visuomotor tasks (Petrides, 1982; Rizzolatti et al., 1983), as does severance of its connections with the areas that provide its sensory afferents (Keating, 1973; Haaxma and Kuypers, 1975).

Numerous cells in the premotor cortex exhibit sustained activity before the execution of a movement (Wise et al., 1983; Weinrich et al., 1984) called set activity. When the instruction cue stops being visible but the instruction itself is not recalled (i.e. the subject is still expected to perform movement towards the same target) the set

activity remains unchanged. However when the instruction cue is replaced by a new one that invalidates the previous one (i.e. the subject is expected to execute movement towards a different target) the set activity is altered (Wise and Mauritz, 1985). This discharge pattern is compatible with activity that reflects movement preparation (Wise, 1985)

It was recognized from early cytoarchitectonic studies (Von Bonin, 1947) that the premotor cortex could be further subdivided. Matteli et al (1985) used the laminar pattern of cytochrome oxidase activity to refine the demarcation of those areas. The mesial premotor cortex corresponding to Woosley's supplementary motor area is subdivided to the caudal SMA proper (F3) and the rostral pre-SMA (F6) (Luppino et al., 1991). Area F7 corresponds to the rostal part of the dorsal premotor cortex and contains the supplementary eye fields (Schlag and Schlag-Rey, 1987), while area F2 represents the caudal dorsal premotor cortex. Area F2 as defined by Matelli matches better the extent that physiological studies of Wise et al. (Wise et al., 1997) describe than the area 6DC of Barbas and Pandya (Barbas and Pandya, 1987). This part of the premotor cortex receives input from the parietal areas PEc, medial intraparieral area (MIP) and less prominently from ventral intraparietal area (VIP). Contrary to areas F7, F3 and F6, area F2 sends direct projections to both primary motor cortex (area M1) and the spinal cord (Dum and Strick, 2002). Microstimulations with parameters that are traditionally used for M1 studies fail to elicit movements in F2 (Weinrich and Wise, 1982), but longer trains of higher current intensity (up to 60 μA) can produce movements (Godschalk et al., 1995). Raos et al (2003) used currents up to 40μA and train durations of up to 100ms and obtained movements in 43% of the area F2 stimulation sites (in comparison, 94% of M1 sites produced movements). These stimulations showed a distinct somatotopic organization of area F2, where proximal movements are represented medially, distal movements are found laterally and more complex movements are elicited anteriorly, close to the arcuate sulcus. Neurons of the premotor cortex are classically described as exhibiting discharge before and during the execution of reaching movements (Caminiti et al., 1991; Kalaska et al., 1997; Wise et al., 1997). However it's worth noting that F2 also contains representations for distal movements that are selective to wrist orientation and distinct types of grasps (Raos et al., 2004).

The ventral premotor cortex (PMv) is located ventrally to the spur of the arcuate sulcus and is furtherly subdivided in area F4, caudally, and the more rostral area F5 (Matelli et al., 1985). Both areas have direct projections to the spinal cord (Dum and Strick, 2002). Area F4 receives input from the parietal area VIP (Luppino et al.,

1999). Microstimulation elicits hand, arm, trunk, neck, face and mouth movemenents, somatotopicaly organized with axial movements represented caudally, distal movements more rostrally and mouth movements laterally. However, the somatotopy is more fragmented and less clear-cut that the one observed in the primary motor cortex as for example face and arm movements can be represented in the same regions (Gentilucci et al., 1988). Graziano et al (2002) performed microstimulations of exceptionally long duration in area F4 and obtained complex and seemingly purposeful movements. F4 neurons discharge for movements towards and away from the body, mouth or face movements and exhibit sensory receptive fields that are tactile, tactile and visual (bimodal neurons) and, less frequently, visual (Gentilucci et al., 1988; Graziano et al., 1997). This pattern of activity is compatible with the notion that area F4 is encoding movements within the peripersonal space (Fogassi et al., 1996).

More rostrally, in and behind the inferior limb of the arcuate sulcus, lies area F5. Area F5 receives afferents from the parietal area AIP (Luppino et al., 1999). The majority of the F5 neurons discharge for movements of the distal portion of the forelimb. Those neurons discharge before movements of either hand and discharge selectively for the type of grip employed, namely precision grip, finger prehension or whole hand prehension (Rizzolatti et al., 1988). Observation of three dimensional object elicits responses from F5 neurons (Murata et al., 1997) and often there is a relationship between the shape of the object and the type of prehension the neuron also discharges for (Raos et al., 2006). More importantly, F5 contains neurons that discharge for observation of a purposeful actions as well as for their execution. (di Pellegrino et al., 1992; Gallese et al., 1996; Rizzolatti et al., 1996). These neurons, named 'mirror neurons', have excited particular interest for their potential role in action understanding, imitation (Rizzolatti et al., 2001), understanding intentions (Fogassi et al., 2005), empathy, theory of mind (Gallese and Goldman, 1998) and language acquisition (Rizzolatti and Arbib, 1998).

It is worth noting that while the PMv is associated with the control of distal movements and grasping actions (Rizzolatti et al., 1988; Jeannerod et al., 1995), proximal movements are also represented. Thus, a complete representation of limb movements is found in the PMv (Stark et al., 2007; Takahashi et al., 2017). This is also evident from microstimulations studies that did evoke arm movements from the ventral premotor cortex (Godschalk et al., 1981; Stark et al., 2007). In line with the above observations, functional imaging with ^{14}C deoxyglucose also documented increased metabolic activity in area F5 during the execution of visually guided reaches (Gregoriou and Savaki, 2003).

Frontal areas involved in eye movement control

In close proximity to the premotor cortex—just anterior to it—lies an area with major role in the control of the eye movements, the frontal eye field. The frontal eye fields were discovered by Ferrier who elicited contralateral eye movements when he electrically stimulated a region in the prefrontal cortex of several macaques (Ferrier, 1876). The location and extent of this cortical area were subsequently defined as the prefrontal region where minimal electrical currents evoke eye movements (Robinson and Fuchs, 1969; Bruce et al., 1985). Bruce & Goldberg (Bruce et al., 1985) set as threshold currents of maximum 50μA and refined the extent of the FEF as having its caudal margin in the fundus of the arcuate sulcus and occuping both limbs of the anterior bank of the arcuate sulcus and extending a few millimeter on the surface of the prearcuate gyrus. This functionally defined region does not have an exact correspondence with cytoarchitectonicaly defined areas. The lateral portion of the prearcute gyrus is assigned to area 45, the central and medial portion of the prearcute gyrus as well as the top part of the anterior bank of the arcuate sulcus corresponds to part of the area 8A (Walker, 1940).

The low threshold FEF is coextensive with an area containing higher concentrations of large layer V pyramidal neurons (Stanton et al., 1989). Horseradish peroxidase (HRP) staining showed that the FEF projects to the superior colliculus (Komatsu and Suzuki, 1985). It also projects to other subcortical loci such as to the striatum of the basal ganglia, the subthalamic nucleus, the thalamus (especially to the mediodorsal nucleus; Giguere and Goldman-Rakic, 1988), the mesencephalon (e.g. the rostral interstitial nucleus of the medial longitudinal fasciculus, the interstitial nucleus of Cajal) and pontine nuclei (e.g. the nucleus reticularis tegmenti pontis, the dorsal raphe, the paramedian pontine reticular formation; Stanton et al, 1988;Huerta et al, 1986). Most of the subcortical connections of the frontal eye fields are known to have visuomotor roles and most of them also receive direct projections from the deeper layers of the superior colliculus (Huerta et al., 1986). The FEF is reciprocally connected with the rostrally located periprincipal area, the supplementary motor area ipsilaterally and contralaterally, the contralateral FEF and caudally to the ipsilateral adjacent premotor cortex (Barbas and Mesulam, 1981; Huerta et al., 1987). It also receives input from the visual areas LIP (lateral intraparietal), MT (middle temporal), MST (medial superior temporal), TEO (temporoccipital) and TE and more weakly from areas V4, V3 and V2 (Schall et al., 1995).

The importance of the FEF in eye movement generation was highlighted by inactivation experiments. Ablation of both the superior colliculus and the frontal

eye fields produces loss of saccadic movements towards peripheral targets (Schiller et al., 1980). Ablation of the FEF produce deficits in memory guided saccades. (Dias and Segraves, 1999). Inactivation of the FEF also produces increased latency and decreased saccadic velocity, which are recovered with time (Schiller and Chou, 2000). Larger saccades are also affected the most during those inactivation studies (Sommer and Tehovnik, 1997).

The electrophysiological properties of the neurons in the FEF underscore their role in transforming sensory information into eye movements. A large portion of the population exhibits presaccadic discharge. Those are furtherly classified into visual, movement and visuomovement, with the last category exhibiting a continuum of profiles where either visual or motor activity is more pronounced. There are also neurons with postsaccadic activity, neurons that are sensitive to the position of the eye, fixation neurons, neurons that discharge during smooth pursuit and neurons responsive to auditory stimuli (Bruce and Goldberg, 1985). The subpopulation that projects to the superior colliculus is composed mainly by movement and fixation neurons with far fewer visual and postsaccadic neurons (Segraves and Goldberg, 1987). Visual neurons have relatively tight tuning fields in regards to directional selectivity compared to movement neurons which have almost twice wider tuning fields and are considered to encode movement as a population. About one in five cells with movement related discharge exhibited also anticipatory activity. (Bruce and Goldberg, 1985).

Caudal to the FEF, at the fundus and the posterior bank of the monkey arcuate sulcus lies an area where intracortical microstimulation with currents less than 50 μA evokes smooth pursuit movements with currents of higher intensity producing movements of higher velocity (MacAvoy et al., 1991). Accordingly, this site contains neurons that discharge before and during smooth pursuit movements (MacAvoy et al., 1991; Fukushima et al., 2000). Ablations that include the arcuate fundus produce deficits is smooth pursuit generation (Keating, 1991; Keating et al., 1996).

Within the dorsal premotor cortex, just laterally to the SMA, there is an area where microstimulation can elicit saccades with currents lower than 50 μA (Schlag and Schlag-Rey, 1987). This area, called the supplementary eye field (SEF), lies within area F7 and sends projections to the major oculomotor centers, the FEF and the superior colliculus (Huerta and Kaas, 1990; Shook et al., 1990; Schall et al., 1993). The SEF have many common afferent and efferent connections with the FEF (Tehovnik et al., 2000). Lesions to SEF produce subtle effects and do not impair the subjects ability to fixate at visual or remembered targets. Deficits were apparent in a task requiring two sequential remembered saccades (Sommer and Tehovnik, 1999). Moreover lessions of SEF caused disturbances in target selection, albeit much more subtle than

the ones observed following FEF lesions (Schiller and Chou, 1998). SEF neurons exhibit discharge relating to saccades (Schlag and Schlag-Rey, 1987). Saccade related activity could be phasic before saccades towards a visible or remembered target, set related activity, sensory related or post saccadic discharge (Schall, 1991a). SEF neurons may also discharge during target tracking with smooth pursuit movements, in a way that the predictability of the target movement is represented in the discharge (Heinen, 1995; Heinen and Liu, 1997). SEF neurons can encode reward for a saccadic option that is depended on the task setting, so one of the roles attributed to this area is that of assigning context-dependent action value (So and Stuphorn, 2010)

Eye related signals in the premotor cortex

The rest of the premotor cortex, despite its well-documented role in the control of skeletal movements has also been found to exhibit gaze related activity. Functional imaging with ^{14}C deoxyglucose has been used to evaluate the glucose metabolism in the monkey cortex during the execution of saccades (Moschovakis et al., 2004; Savaki et al., 2015). In these studies, there was a frontal region of high metabolic activity that encompassed, predictably, the FEF, but also extended caudally into the posterior bank of the arcuate sulcus into the premotor areas F2 and F5. Functional magnetic resonance imaging studies on monkeys executing visually guided saccades provided similar results; increased activity that extended beyond the fundus of the arcuate sulcus into the premotor cortical areas located in the posterior arcuate bank (Koyama et al., 2004; Baker et al., 2006).

Extracellular recordings have shown that premotor neurons have discharge that is sensitive to gaze position. Boussaoud et al (1993) found neurons in the ventral premotor cortex whose response to visual stimuli was dependent on the position of the eyes in the orbit, in such a way that in some gaze positions the visual discharge was diminished and in others completely eliminated. Such gaze effects in the ventral premotor cortex have been observed during visually guided reaches as well; the intensity of the phasic movement related discharges of 41% of these cells depended on the eye position in the orbit (Mushiake et al., 1997). Similar observations have been made for the dorsal premotor cortex as well. The majority of dorsal premotor neurons exhibit such gaze position effects (79%) during their set related activity before reaching movements. Gaze position may enhance, attenuate or reverse the neurons directional tuning. (Boussaoud, 1995). When the instruction cue for a movement is presented at a certain retinal eccentricity, the activity of almost three quarter of the respondent PMd neurons was affected by the angle of the gaze. The phasic discharge during movement execution is also modulated by gaze position in

four fifths of the dorsal premotor neurons. (Boussaoud et al., 1998). Cisek and Kalaska (2002) studied the gaze modulation during reaches with unrestricted eye movements. They, too, report modest but statistically significant gaze modulation in 27% of the PMd cells during the observation of the instruction cue, in 51% of the cells during the delay period preceding reaches and in 60% of the cells during reaches.

Pesaran et al (2006) studied the set related discharges of neurons in the dorsal premotor cortex and the parietal reach region by employing a behavioral paradigm that entailed reaching movements towards different positions from different hand initial positions while the gaze was fixated at different angles. The majority of the PMd cells discharged in a way that the representation of hand, eye and target positions were inseparable, i.e. neurons encoded simultaneously target in respect to hand position, target in respect to eye position and eye position in respect to hand position. The parietal reach region also contained such cells, but there far more neurons encoded target position in respect to just gaze orientation. A similar behavioral paradigm was employed by Batista et al (2007) for the set discharge of dorsal premotor neurons. They encountered some neurons with discharge sensitive just to eye position, others sensitive just to initial hand position, but the majority of cells were encoding both eye and hand positions (86 out of 154 cells).

Mushiake, Boussaoud, Pesaran and Batista, all discuss their findings in the context of the frame of reference transformations required for visually guided reaches. To generate a movement towards a visible target, the vector of the target location and the vector of the end effector position have to be encoded in the same frame of reference. Then the desired movement (the motor error vector) can be easily calculated as the difference of the two vectors. Earlier studies considered that the cortex encoded movements in a shoulder or body centered coordinate system (Caminiti et al., 1991; Flanders et al., 1992; Fogassi et al., 1992; Andersen et al., 1993). This representational scheme means that the location of the target is first, using retinal location and gaze orientation signals, transformed to body centered coordinates and this transformed target location is, then, used for the motor planning step. However, the presence of gaze related signals in the premotor cortex is evidence that reaching movements are planned, instead, in a fixation centered coordinate system (Mushiake et al., 1997; Boussaoud et al., 1998; Pesaran et al., 2006; Batista et al., 2007).

This gaze modulation of reach related discharges could account for the saccade related activity that the functional imaging studies noted in the premotor cortex. Interestingly, premotor cells do discharge before saccades as well. Tanaka and Fukishima (1998) in a study of the smooth pursuit activity in the periarcuate cortex, also reported numerous neurons in the posterior bank of the arcuate sulcus that discharged before saccades. Pesaran et al (2010) in a follow up study studied the set

related activity of dorsal premotor and parietal neurons during saccades with varying initial eye and hand configurations. They encountered 37 out of a total of 174 premotor neurons with discharges exclusively for saccades and 66 cells that had activity relating to both reaches and saccades. They found that premotor neurons had stronger discharges for saccades and employed the relative position frame of reference encoding they reported for their reach related cells. Despite the fact that their study focused on the set related activity during the delay epoch, the examples they provide show that the saccade related activity of cells in the premotor cortex can very well include a strong phasic movement related discharge. Such phasic discharges before saccades in the dorsal premotor cortex were encountered by Fujii et al (2000) as well. 104 out of 541 movement related dorsal premotor cells had movement related responses for both saccades and reaches and 66 cells had activity only during saccades. The majority of the cells that exhibited saccade related activity were located in the rostral premotor cortex (about 73%). Ventral premotor cortex too contains such neurons, as Fujii et al (1998) in another study recorded there 102 neurons with activity before and during saccades, 36 of which discharged exclusively before saccades.

This saccade related activity in the premotor cortex has not been necessarily interpreted as involved in saccade generation. For example, Pesaran et al (2010), commenting on the fact that PMd contains stronger saccade related activity than parietal reach region, proposes the FEF or the SEF as the source of those signals. So, they regard the nature of the saccade related activity as efference copies from the frontal oculomotor areas that facilitate the process of encoding limb movements in a fixation centered coordinate system. These frontal areas, indeed, project to the premotor cortex (Huerta et al., 1987; Huerta and Kaas, 1990) and may very well transmit such signals there. However, there is evidence in favor of a role of the premotor cortex in saccade generation. Moschovakis et al (2004) used retrograde transynaptic transport of rabies virus to identify regions oligosynaptically connected to the lateral rectus muscle of monkeys. In the periarcuate region retrograde traces could be found, as expected, in the FEF. Surprisingly, dense concentrations of tracers were located in the posterior bank of the arcuate sulcus, especially in the vicinity of the spur of the arcuate sulcus. Fujii et al (1998) could elicit saccadic movements with currents ranging from 40 to 80 μA from the rostral part of the dorsal premotor cortex. In their ventral premotor cortex study they also managed to elicit eye movements. The PMv sites where the intracortical microstimulations produced eye movements were concentrated in a particular area in the cortical convexity, which was topographically disjoint from the FEF and which they named PMVe.

AIM OF THE STUDY

The purpose of our project was to explore if the premotor cortex can generate eye movements, coordinate them with hand movements and participate in the decision process of effector selection. To this end, we conducted extracellular recordings from the premotor cortex and the FEF in behaving rhesus monkeys that captured peripheral targets using eyes, hands or coordinated eye-hand movements. Contrary to past studies of eye related discharges in the premotor cortex, we focused on the portion of the activity that was more causally relevant to movement generation, namely the phasic discharge just before and during movements. Evaluating the temporal and spatial activity profiles of the FEF and premotor neurons in relation with behavioral events allowed us to a) compare FEF to premotor saccade related discharges b) assess the degree of coupling of the premotor discharge to the onset of eye and hand movements and c) examine if a common signal for eye and hand movements exists in the premotor cortex, i.e. if there are premotor neurons, whose discharge precedes both saccades and hand movements and is also temporally coupled to both of them.

We also performed intracortical microstimulations in FEF and the premotor cortex. This approach enabled us to examine if the caudal bank of the arcuate sulcus and its spur can generate eye movements. Finally, we examined if the saccades evoked from premotor sites differ from those elicited from the FEF.

METHODS

Animal preparation

We obtained data from three hemispheres of two adult female rhesus monkeys (*macaca mulatta*), weighing 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 Institutional 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. They were surgically prepared for painless head immobilization, eye position monitoring and extracellular recording under anesthesia and aseptic conditions. For head immobilization, a metal bolt was cemented onto mandibular plates secured on the cranium with titanium screws (Synthes, Bettlach, Switzerland). After completion of the training, and following craniotomy, a metal chamber (Christ Instr., Damascus, MD) of 1 cm in radius was cemented onto the bone at stereotaxic coordinates appropriate for lowering electrodes in the arcuate sulcus. In between recording sessions, a gel containing antibiotic (Tobramycin 0.3%) was applied on the dura and the chamber was capped. To monitor eye movements (Robinson, 1963), a scleral search coil (AS633 Cooner wire, Chatsworth, CA) was sutured on the sclera (modified from Judge, 1980).

Behavioral paradigm

Monkeys were trained for 3-6 months till they successfully completed more than 90% of the trials. To perform their tasks, subjects sat in a primate chair in the dark, facing a 21'' 120Hz monitor (MicroTouch 3M, St. Paul, MN) positioned 27 cm in front of their head. The latter was centered within two orthogonal magnetic fields generated by currents alternating at 50 kHz 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) with a resolution of 0.1° and noise level 0.3° peak to peak. Its gain was

calibrated frequently, by averaging at least 10 movements in each direction after asking the animal to execute a series of vertical and horizontal movements of 10° amplitude centered on straight ahead.

Targets were white, circular (1.5 deg in diameter) and they were presented on the video monitor. A water delivery tube was attached close to their mouth, and successful completion of each trial was rewarded with drops of water. Hand tasks were performed with the forelimb contralateral to the hemisphere we recorded from. As in previous studies (e.g., Boucher et al, 2007), subjects handled a two-dimensional joystick (ETI systems, Carlsbad, CA) that controlled the position of a cursor (a white open circle of 1° diameter) on the video display. Subjects were seated with their forearms in a roughly horizontal orientation (elbow flexed 90°) and resting comfortably on plastic supports that were attached to the primate chair while their hand grasped the vertically oriented handle of a joystick that rested on the same support. Movement of the joystick was accomplished with a combination of arm, forearm and wrist movements. No force had to be exerted to keep the joystick in its central position. The gain of the joystick was adjusted so that its displacement by 9 mm corresponded to the displacement of the cursor on the screen by 10° and a force of 0.58 N had to be exerted to keep the cursor stationary at such an eccentric position. Ambient illumination and chair construction was such that the subject was prevented from viewing the working forelimb. Eye position and joystick output were sampled at rates of 1000 Hz and 666 Hz, respectively, with an 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 off-line analysis. A PC running custom behavioral control software and equipped with an Advantech (Taipei, ROC) analog to digital converter also sampled the eye and hand movements at 120Hz, displayed the visual elements of the tasks and controlled online the behavior of the subject in relation with the demands of the tasks. Figure 1 provides a diagrammatic outline of the experimental setup used.

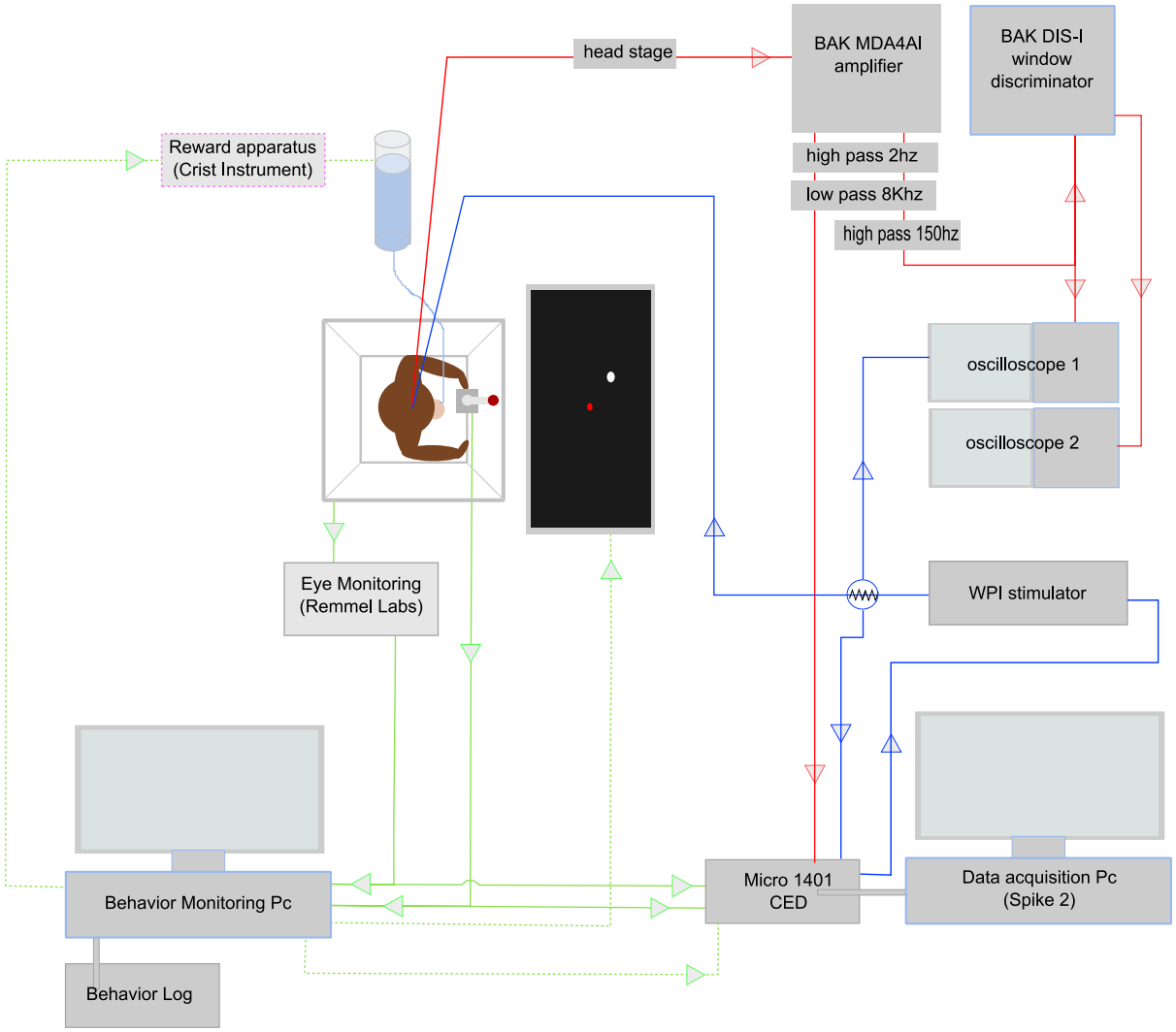

Figure 1 Diagram of the experimental setup. Red arrows indicate the flow of signals from the extracellular recordings, green arrows indicate the handling of behavioral data and blue arrows denote the flow of triggers and signals used for the intracortical microstimulations.

Subjects performed center-out tasks using their eyes, their hand or both. Figure 2 illustrates the tasks we employed. Each trial started with the appearance of a white fixation disk in the center of the screen, which, after 200-300ms changed color depending on the effector (instruction cue) that had to be used in the successful completion of the trial (red for saccades, purple for hand movements, blue for coordinated eye-hand movements). After another 200-300ms, a peripheral target (1° diameter) appeared in one of 8 different directions (0°=right, 45°=right-up, 90°=up, 135°=up-left, 180°=left , 225°=down-left , 270°=down, 315°=down-right) and at a

distance of 10° or 20° away from the fovea. After a variable delay (300-1200ms), the fixation point turned into an open circle (the go cue) of the same diameter and color as the fixation solid circle, and the subject had to execute a movement toward the target using the effector(s) prescribed by the color of the fixation point. After acquiring the target, the animal had to keep the effector(s), eye, hand or both, for 200ms within a square window 1.5 deg on the side surrounding the target's center, for the trial to be considered successful and the subject rewarded with a drop of liquid delivered through a computer controlled valve (Crist instruments, Damascus, MD). In cases where the animal moved the wrong effector, or the movement metrics were wrong (i.e., the effector landed outside the square window surrounding the target's center) or if the movement was not completed within 0.6 sec for eye movements and 1.2 sec for hand movements, the trial was aborted and there was no reward. In another task, the subject had to execute a rapid eye movement to the memorized location of a flashed target. This task was similar to the visually guided saccade task in all aspects except that the peripheral target was shown for 200 ms. Its disappearance was followed by a delay period of 300-1200 ms at the end of which the subject had to execute a saccade to the memorized location of the briefly flashed target to be rewarded. Finally, the fixation task, shown at the bottom of Fig. 2, started with the display of a "fixation" solid white circle at the center of the screen, which turned into an "instruction" green solid circle within 200-300 ms. A peripheral target appeared after a variable delay (200-300 ms) and a cursor identical to the one employed in the hand task appeared 300-600 ms later and moved for 500 ms towards the peripheral target. Following the end of the cursor movement and after a variable delay (200 – 400 ms), the fixation point turned into an open circle similar to the go cue. The subject had to keep its gaze fixed for an additional 500 ms at the end of which it received its reward.

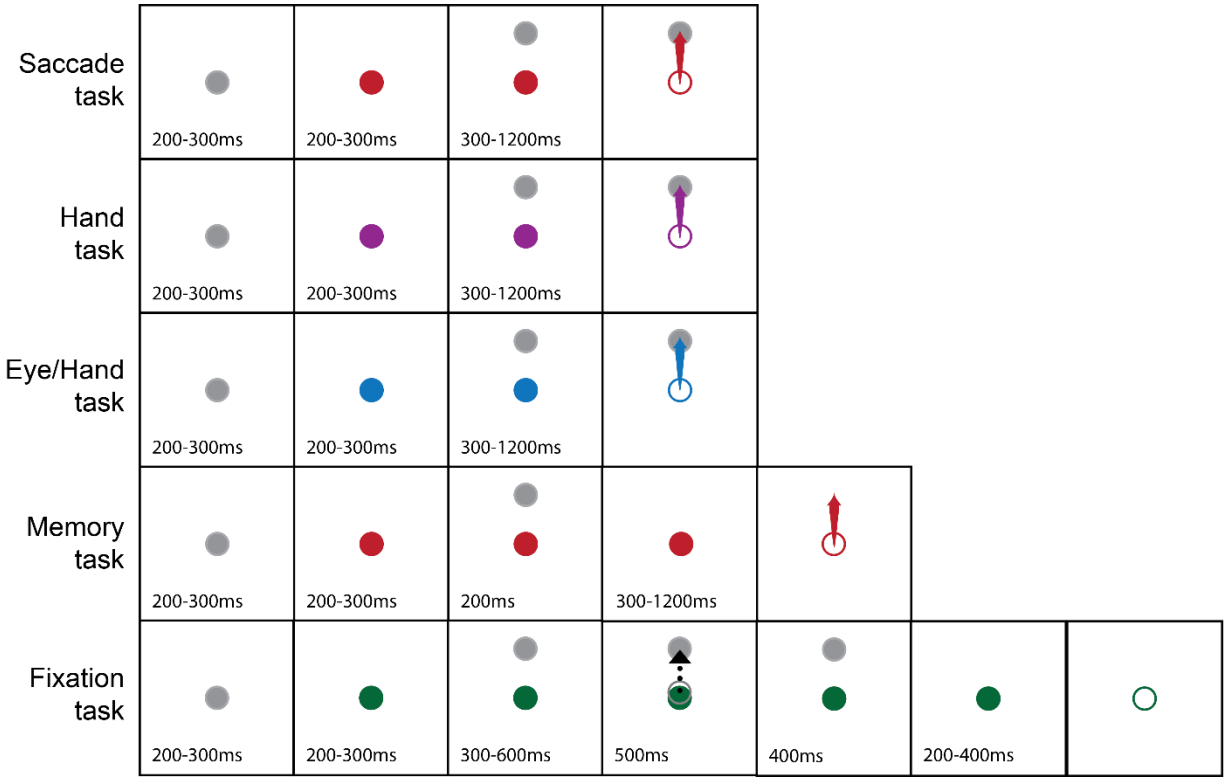

Figure 2. Pictorial summary of the behavioral tasks we used. The gray fixation point turned into a color (solid circle) to instruct the subject on the effector to use (Red: Eye; Purple: Hand; Blue: Both the eyes and the Hand; Green: Hold fixation) to capture a peripheral target (arrow). The dashed black arrow indicates cursor movement in the fixation task. Open circles indicate the appearance of the Go cue. Numbers indicate epoch duration (in ms).

Data collection

We recorded extracellularly the discharge of single units of the periarcuate cortex of 3 hemispheres contralateral to the moving hand. To this end we used single glass coated tungsten electrodes (AlphaOmega, Nazareth, Israel), of 0.8-1.2 MOhm impedance (measured at 1 kHz frequency), that we slowly lowered through the dura and the cortical gray matter with the help of a hydraulic micromanipulator (Trent-Wells, Coulterville, CA) that was firmly secured on the recording chamber. Electrode signals were amplified (x10,000; Bak Electronics, Inc., Mt. Airy, MD), filtered (band-pass 2 Hz – 10 kHz) and digitized with an A/D converter (CED micro1401-3, Cambridge, UK) at a sampling rate of 20 kHz and stored on disk for off-line analysis.

During microstimulation sessions, the 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 it to direct the subject's gaze towards parts of the oculomotor field. The screen also served to present a series of targets in order to calibrate the gain of the eye monitoring system before collecting data from a site. To calibrate eye position we averaged at least 10 movements in each direction after asking the animal to execute a series of vertical and horizontal visually guided saccades of 10^{o} amplitude centered on straight ahead. Otherwise, the animals were free to move their eyes as they wished. Periods of reduced alertness were reliably identified by a drifting eye position trace and were excluded from analysis.

For the microstimulation sessions, we employed the same electrodes we used for extracellular recordings. Stimuli used to activate the cortex were trains of monopolar pulses (0.25 ms pulse duration) produced by a WPI constant current isolator and driven by the spike2 v5 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 μA - 100 μA) were also used to determine the threshold or ensure 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; Russo and Bruce, 1993; Fujii et al., 2000; Chen, 2006; Knight and Fuchs, 2007; Monteon et al., 2010).

Analysis of extracellular recordings

We used the Spike2 version 5 software (CED, Cambridge, UK) to detect and sort spikes. Spikes belonging to different cells that were recorded simultaneously were separated with the help of the clustering and template matching routines of Spike2. Further, we used custom scripts written in the MATLAB (MathWorks, Natick, MA) environment to analyze spike trains and eye/hand trajectories. Movement onset was defined automatically as the moment when velocity exceeded 20 deg/sec for saccades (Moschovakis et al., 1998), and 1% of maximal velocity for hand movements (Sainburg et al., 1999). Eye velocity (in deg/s) was obtained by numerical

differentiation and smoothing of the instantaneous eye position trace. Hand velocity (also in deg/s) was obtained by numerical differentiation and smoothing of the instantaneous joystick controlled position of the cursor on the screen. Spike trains were transformed into a smoothed version of the instantaneous firing rate function, $R_n=5/(t_{n+3}-t_{n-2})$. For each spike, occurring at time t_n, we first obtained the running average of five consecutive inter-spike intervals, $(t_{n+3}-t_{n-2})/5$, two before and three after the spike in question. R_n was obtained from the inversion of this running average inter-spike interval. We aligned the instantaneous firing rate functions of single trials on movement onset and evaluated the median value from all the trials to the same target. Then the instantaneous firing rate function was normalized to express it as multiples of standard deviation (SD) away from the mean rate -μ- of discharge during the reference period (defined as the period ending with the go cue and starting 300 ms before its appearance) of all trials where movement was executed toward the same target with the same effector(s). Discharge onset for a particular trial was defined as the time when instantaneous firing rate exceeded reference discharge by 2 SD. Onsets were visually checked and corrected when necessary. Because for many of the neurons we describe, discharge onset varies with movement direction, the discharge latency we refer to in this study is the one obtained for movements in the neuron's preferred direction.

To be included in this study the onset of a neuron's discharge had to precede the onset of saccades or the onset of the hand movements. Furthermore, the intensity of its discharge during the movement epoch (ME) had to exceed significantly (unpaired t-test) that of its discharge during the reference period. Since the eyes and the hand did not move simultaneously and to minimize contamination with delay period activity or post-movement activity, we considered the hand related ME to include the time interval from 100 ms before until the onset of the hand movement in hand and eye/hand trials (in the case of Meq cells the ME was defined as -60 ms before to 20 ms after the hand movements). Similarly, we considered the saccade related ME to include the time interval from 30 ms before until 30 ms after the onset of saccades in eye and eye/hand trials.

Each cell's directional tuning was determined from the goodness of fit of its firing rate to a circular Gaussian (von Mises) distribution. Briefly, we, first, calculated the mean firing rate of all trials during movement of each effector towards each target. The firing rate (R) above reference activity (mean rate in the period 300 ms before the go cue), was fit with the expression $A\frac{e^{k\cos(x-\mu)}}{2\pi I_o(k)}$ where A is a scaling factor,

μ the unit's preferred direction, *k* a measure of field width defined as $2/\sqrt{k}$ and $I_o(k)$ the modified Bessel function of order 0. Unpaired t-test between the discharge within this period of time and the baseline discharge was used to decide if the neuron discharge increased for movements of each effector to each target position. We employed the Watson-Williams test, to evaluate if a cell had a different preferred direction for eye and hand movements and the Rayleigh test to check if the preferred directions were uniformly distributed in a population of neurons. Both tests were part of the circular statistics toolbox (Berens, 2009)).

To obtain a measure of the duration of neuron discharge, we estimated its half-width defined as the time period between the first rise of instantaneous firing rate above values higher than half way between the baseline and the peak rate and the first drop below the same value after reaching the peak. The duration of discharge of the neuron for each effector was defined as the mean value of the discharge durations of all targets where that discharge significantly exceeded the reference discharge (as indicated with a t-test). The peak rate of discharge within this period of time was also measured to analyze, on a trial by trial basis, its relationship with the peak velocity of movements towards the preferred target and, depending on field width, neighboring targets as well. The targets selected were always at the same eccentricity. To assess the temporal relationship between the onset of the discharge and the onset of effector movement we used linear regression and tests of homoscedasticity (Bartlett's and Kepner-Randles tests). The null hypothesis in the Kepner-Randles test is that the data is distributed in a symmetric bivariate manner and the test detects unequal marginal scales. It has the advantage of being non-parametric and does not depend on the value of the mean. A fairly detailed description of the algorithms used in it can be found in (Kutz et al., 2003). For t-test/ANOVA, Wilcoxon, Bartlett's test, linear regression, and curve fitting we used functions contained in the MATLAB statistical toolbox (Berens, 2009).

Analysis of microstimulations

We used the Spike2 version 5 software (CED, Cambridge, UK) to analyze saccades. Eye velocity and saccade onset were obtained by the same methods described in the *analysis of extracellular recordings* section. Onsets were visually checked and corrected when necessary. Saccades with latencies >80ms 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

We made small injections of Biotinylated Dextran Amine (10 kDa) and placed electrolytic lesions in the right hemisphere of one of the monkeys we studied shortly before its perfusion. The subject was killed with an overdose of pentobarbital and perfused with saline followed by a buffered solution of formaldehyde, glutaraldehyde and picric acid. After the end of the perfusion, the brain was photographed *in situ* at a plane parallel to that of the recording chamber (30 degrees medial and 15 degrees caudal). It was then blocked frontally, 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.

Decoding

Feed-forward artificial neural networks have been used before to decode motor behavior from the discharge pattern of frontal lobe neurons (Hatsopoulos et al., 2004; Ben Hamed et al., 2007). Here, we built a three layer feedforward artificial neural network, to explore if the discharge pattern of Meq cells could be decoded in a way that would allow specification of movement direction as well as of the effector that would execute it. The output of each one of its units (y_i) equaled $tanh(\sum w_{ij}x_j)$ where x_j are the units driving $y_i$and w_{ij} the connection strengths between units x_j and y_i. The hidden layer comprised 100 units and the connections between them were initially set randomly to values between -1 and 1. The input layer was made of 55 units each one of which was supplied with a number indicative of the mean intensity of

discharge of each one of the Meq cells of our sample during the "movement" epoch for an eye movement or a hand movement or a coordinated eye-hand movement. The number in question was selected randomly from all relevant trials for movements of the specific effector in a particular direction. The output layer was made of 8 (when the network decoded movement direction) or 3 (when the network decoded effector identity) units. The target output vector consisted of zeros for the wrong choices and one for the correct choice. To determine if the input vector (i.e., the discharge of 55 Meq units) could specify the movement of the correct effector in the right direction we trained our network using Matlab's scale conjugate gradient backpropagation method (Moller, 1993). Initial weights were shuffled ten times to ensure that the network would not be trapped in a local minimum. Training was performed using 65% of our data set and network performance was evaluated using the remaining 35% of our data. The network was deemed to respond correctly when it could deduce effector and movement direction from the discharge intensities that were supplied to its input layer. The importance of the information carried by groups of Meq cells was assessed by removing a progressively larger number of its members and evaluating network performance after retraining the network

RESULTS

Overview

We recorded the discharges of 525 neurons from three hemispheres of two rhesus monkeys; 417 of these cells discharged in relation to some aspect of the tasks we used. One hundred forty eight of these neurons displayed phasic or sustained visual responses (bonferroni corrected unpaired t-test of cue epoch vs 100-200ms following target presentation) but did not discharge phasically before and during movements of the eyes and/or the hand and were excluded from further analysis. We also excluded another 89 neurons whose discharge increased only after the onset of the movement (bonferroni corrected unpaired t-test of -300 to 0ms pre go vs hold epoch or vs movement epoch and discharge latencies after movement onset). One hundred and eighty cells discharged phasically before and during movements of the eyes and/or the hand.

Figure 3 shows several examples of the 144 neurons we found in the primate premotor cortex whose firing rate transiently increased before and during movements of the eyes and/or hand. To classify all the classes of neurons we compared the ME with the reference pre-GO epoch during hand, eye and eye-hand tasks using bonferroni corrected unpaired t-tests. The top row illustrates the discharge pattern of neurons that emitted phasic discharges before and during saccades and movements of the hand whether accompanied by movements of the other effector or not, which we called motor equivalence neurons (Meq) (Fig. 3A). To be included the onset of their discharge should precede saccades and hand movements in the relevant single effector trials and its intensity in the interval -30 ms before to 30 ms after the onset of the saccades they preferred in saccade trials as well as in the interval -60 ms before to 20 ms after the onset of the hand movements they preferred in hand trials had to be significantly stronger than that in the interval -300 to 0 ms prior to the GO signal. An additional requirement for the Meq cells was that they had discharge in the joint effector task that preceded both saccades and hand movements and had intensity in the interval -30ms before to 30ms after the onset of saccades they preferred that was significantly stronger that the activity in the interval -300 to 0 ms prior to the GO signal. Some neurons (Fig. 3B) discharged vigorously before and during saccades in certain directions whether these were accompanied by hand movements or not (S neurons). To be included in this class, the onset of their discharge (defined in the

Methods section) had to precede the onset of saccades and its intensity in the interval -30 ms before to 30 ms after the onset of the saccades they preferred had to be significantly stronger than that in the interval -300 to 0 ms prior to the GO signal in both the saccade and the eye-hand trials. Other neurons (Fig. 3C) discharged for hand movements in certain directions whether these were accompanied by saccades or not (H neurons). To be included in this class, the onset of their discharge had to precede the onset of hand movements and its intensity in the interval -100 ms to 0 ms before the onset of the hand movements they preferred had to be significantly stronger than that in the interval -300 to 0 ms prior to the GO signal in both the saccade and the eye-hand trials. The interval –100 to 0 ms relative to the onset of hand movements has been shown to work well in hand related cells of the ventral premotor cortex (Kakei et al., 2001). A small number of cells (Fig. 3D) discharged for saccades in certain directions only if these were not accompanied by hand movements (xS neurons). To be included in this class, the onset of their discharge had to precede the onset of saccades while its intensity in the interval -30 ms before to 30 ms after the onset of the saccades they preferred had to be significantly stronger than that in the interval -300 to 0 ms prior to the GO signal in saccade trials but should not increase appreciably in the eye-hand and the hand trials. Another group of equally sparse cells (Fig. 3E) discharged for hand movements in certain directions only if these were not accompanied by saccades (xH neurons). In their case, discharge onset should precede hand movement onset and the intensity of their discharge in the interval -100 ms to 0 ms before the onset of the hand movements they preferred had to be significantly stronger than that in the interval -300 to 0 ms prior to the GO signal in hand trials but should not increase in saccade and eye-hand trials. Figure 3F illustrates a cell that discharged for coordinated eye-hand movements in certain directions but not when the same movements were executed by one of the effectors unaccompanied by movements of the other (AND neurons). To be included in our sample, the onset of their discharge should precede the onset of saccades in eye-hand trials and its intensity in the interval -30 ms before to 30 ms after the onset of the saccades they preferred had to be significantly stronger than that in the interval -300 to 0 ms prior to the GO signal in eye-hand trials but should not change appreciably for saccades in saccade trials or hand movements in hand trials. Finally, a few cells (Fig. 3G) discharged for movements of the eye unaccompanied by movements of the hand and movements of the hand unaccompanied by saccades but not for coordinated eye-hand movements in the same direction (XOR cells). To be included the onset of their discharge should precede saccades and hand movements in the relevant single effector trials and its intensity in the interval -30 ms before to 30 ms after the onset of the saccades they preferred in

saccade trials as well as in the interval -100 ms to 0 ms before the onset of the hand movements they preferred in hand trials had to be significantly stronger than that in the interval -300 to 0 ms prior to the GO signal but should not change appreciably for eye-hand movements in the joint effector trials. The number of cells such as these we encountered in the two animals we studied is shown in Table I. The majority of neurons fell into the S, H, or Meq categories. We now turn to the neurons that discharged shortly before and during saccades in both the eye and the eye-hand task (S neurons).

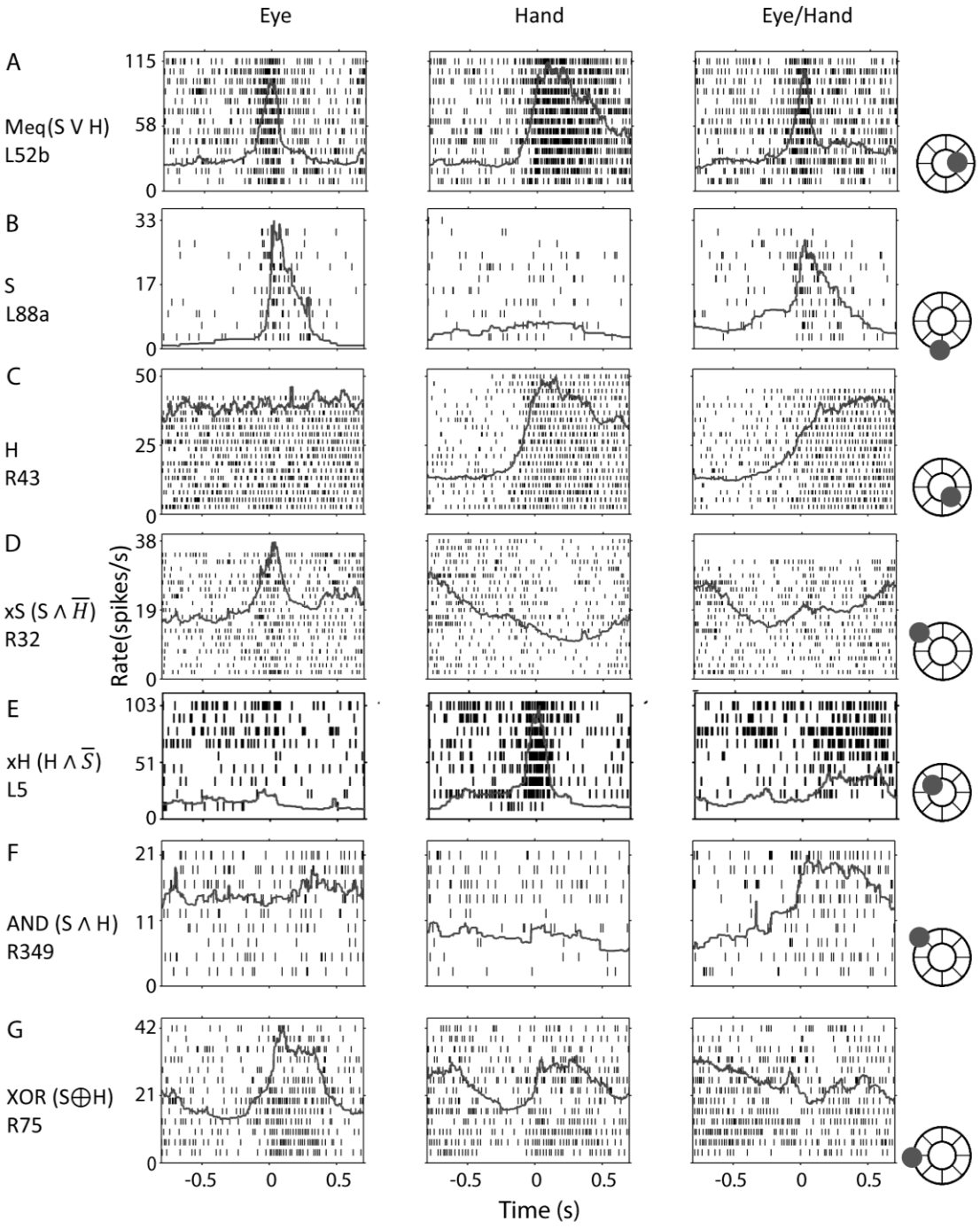

Figure 3. Examples of the 7 classes of neurons associated with saccades and/or hand movements encountered in the premotor cortex of the monkey. Each raster is from a separate trial. They are aligned on the onset of saccades (left column) or hand movements (central column). In the case of eye-hand trials (right column), rasters are aligned either on the onset of saccades (A, B, D, F, G) or hand movements (C, E). The gray line displays the instantaneous firing rate. The gray circle in the cartoon on the right indicates the direction and amplitude of the movements that were accompanied by the discharges displayed. Abscissa: time (s); Ordinate: firing rate (spikes/s).

Cell type	L	R
Meq	27	28
H	5	38
S	9	22
AND	0	2
xS	1	4
xH	3	0
xOR	1	2

Table I. Classification of the movement related neurons we encountered in the primate premotor cortex of subjects L and R based on their discharges in the tasks we employed (Saccade, Hand, Eye/Hand).

Motor equivalence Neurons (Meq)

The present section describes in some detail the phasic, movement related responses of 55 of these cells that discharged before and during coordinated movements of the eyes and the hand as well as movements of one effector not accompanied by movements of the other. Because such cells seem to discharge for the movement executed rather than the effector executing it we refer to them as motor equivalence (Meq) neurons. The same cells also discharged vigorously before memory driven saccades, but not during fixation trials. Thirty-three of them discharged in response to the appearance of a visual stimulus while the remaining twenty-two did not.

Figure 4, illustrates a typical example for movements of 20 deg. The movement field of this Meq neuron remained the same irrespective of the effector employed. To examine quantitatively how closely its preferred direction for saccades fits its preferred direction for hand movements, we measured the average firing rate of this neuron for all trials to all targets during the movement epoch. We fit a von Mises distribution to the data for movements in all directions, separately for different amplitudes (10 deg and 20 deg) and tasks (eye, hand and eye/hand). The on-direction of the neuron shown in Fig. 4, obtained from the von Mises distribution (see Methods), was 290° for saccades, 246° for hand movements and 291° for coordinated movements of the eyes and hand. To determine if the size of the neuron's movement field varied with the effector employed, we compared the values of the parameter $^{2}/_{\sqrt{k}}$ after fitting movement fields with the von Mises distribution as described in the Methods. They did not differ significantly from one task to another measuring 228°, 199° and 185° for eye, hand and eye/hand tasks, respectively.

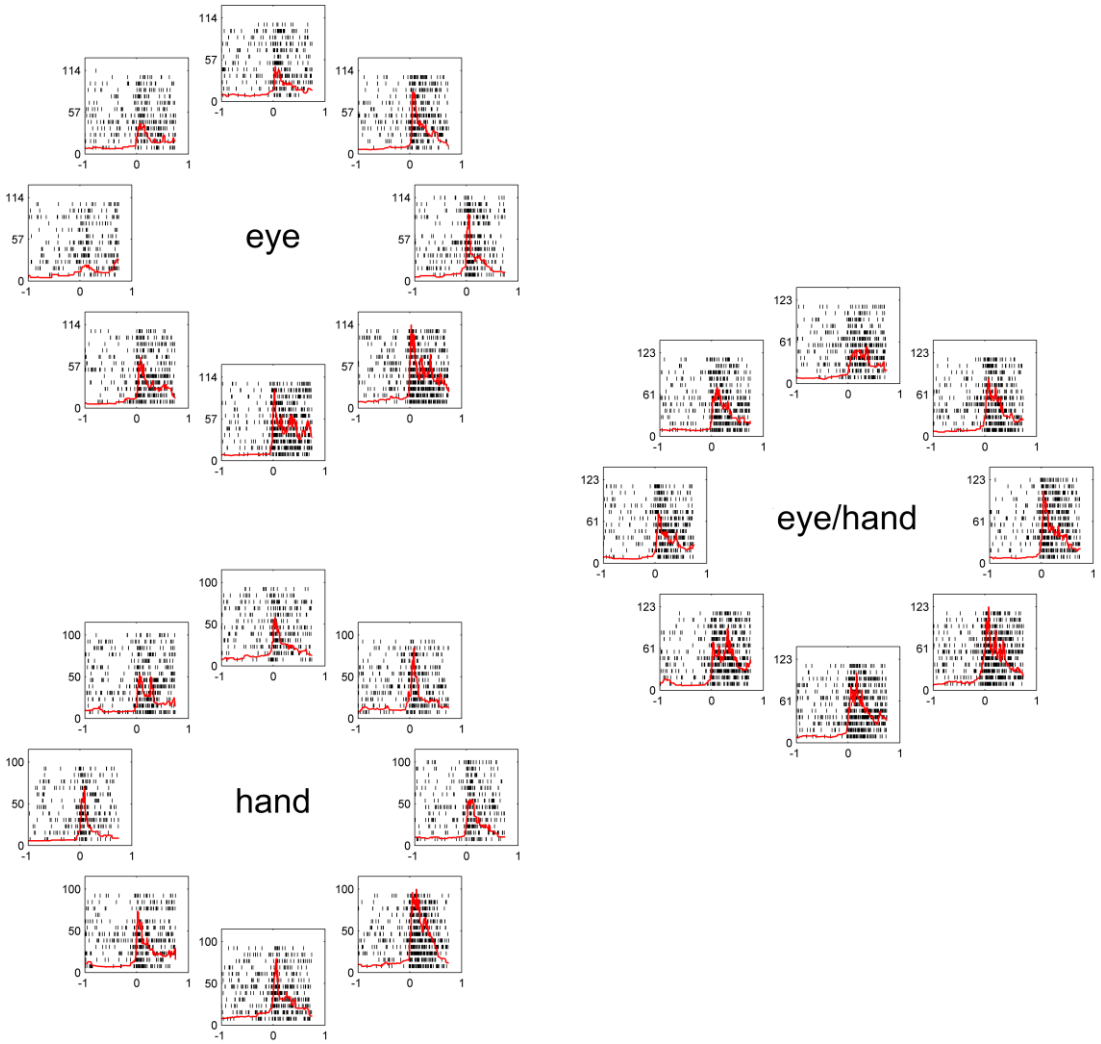

Figure 4. Examples of the discharge pattern of a Meq cell (L89) for 20° movements to visual targets. Movements of 8 different directions have been arranged around the periphery of an imaginary circle, separately for eye, hand and eye-hand trials. Red lines indicate instantaneous firing rate and are aligned on movement onset as are the rasters. Abscissa: time (s). Ordinate: instantaneous firing rate (spikes/s).

Figure 5 illustrates the distribution of the preferred directions of the Meq neurons we encountered. They did not display a preference for contraversive or ipsiversive directions for either the eyes or the hand nor did we find evidence of a departure from the uniform distribution for either effector (Raleigh test: p=0.66 for the hand and p=0.3 for the eye). To examine if the on-direction of a neuron for saccades matched its on-direction for hand movements we measured the angular distance of the two. In about half of the neurons (28/55) this did not differ significantly from zero (such as in the case of the neuron illustrated in Fig. 4) using the Watson-Williams test. Cells such as these are marked "invariant" in the second column of Table II, which summarizes the properties of the discharge of the Meq neurons we encountered.

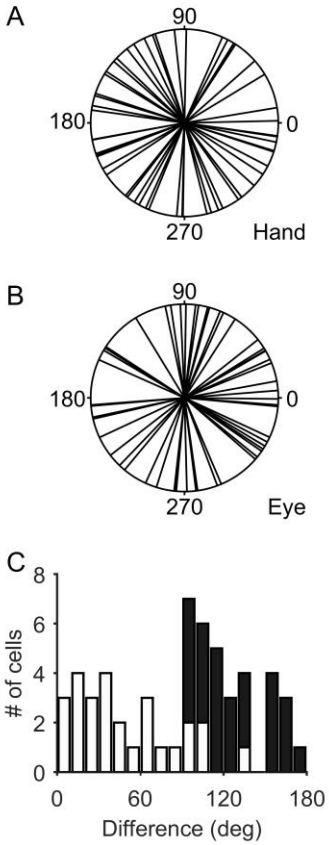

Figure 5. Distribution of the preferred directions of Meq neurons for hand movements (A) and saccades (B). The frequency histogram (C) illustrates the magnitude of the difference between

each neuron's preferred direction for saccades and preferred direction for hand movements. Solid bars indicate statistically significant differences ($p < 0.05$, Watson-Williams).

However, this was not the case in the remaining cells (corresponding to the black bars in the frequency histogram of Fig. 5C). In these cases, we felt it would be interesting to examine if the on-direction of the neuron for eye/hand movements resembles that for saccades or that for hand movements. In fact, both alternatives were realized as shown in Fig. 6. Neuron L42b (Fig. 6, top) discharged for downward hand but preferred upward eye movements. It also discharged for upward movements when both the eyes and the hand moved to the same target. Ten of the neurons we encountered displayed a similar preference during coordinated eye/hand movements and are marked "eye" in the second column of Table II. In contrast cell L45 (Fig. 6, bottom) discharged for rightward eye movements but preferred leftward hand movements while it also discharged for leftward coordinated eye-hand movements. A total of 8 neurons discharged in a similar manner in the eye/hand task and are marked "hand" in the "On-direction" column of Table II. Figure 7 illustrates a neuron whose movement fields for single effector movements did not bear a simple relationship to that constructed from eye/hand movements. It discharged for right-down hand movements and downward eye movements yet it discharged for up-left eye/hand movements. The eye-hand related on-directions of another 5 Meq cells were similar in the sense that they preferred movement directions "intermediate" relative to those for single effector movements and are marked as such in Table II.

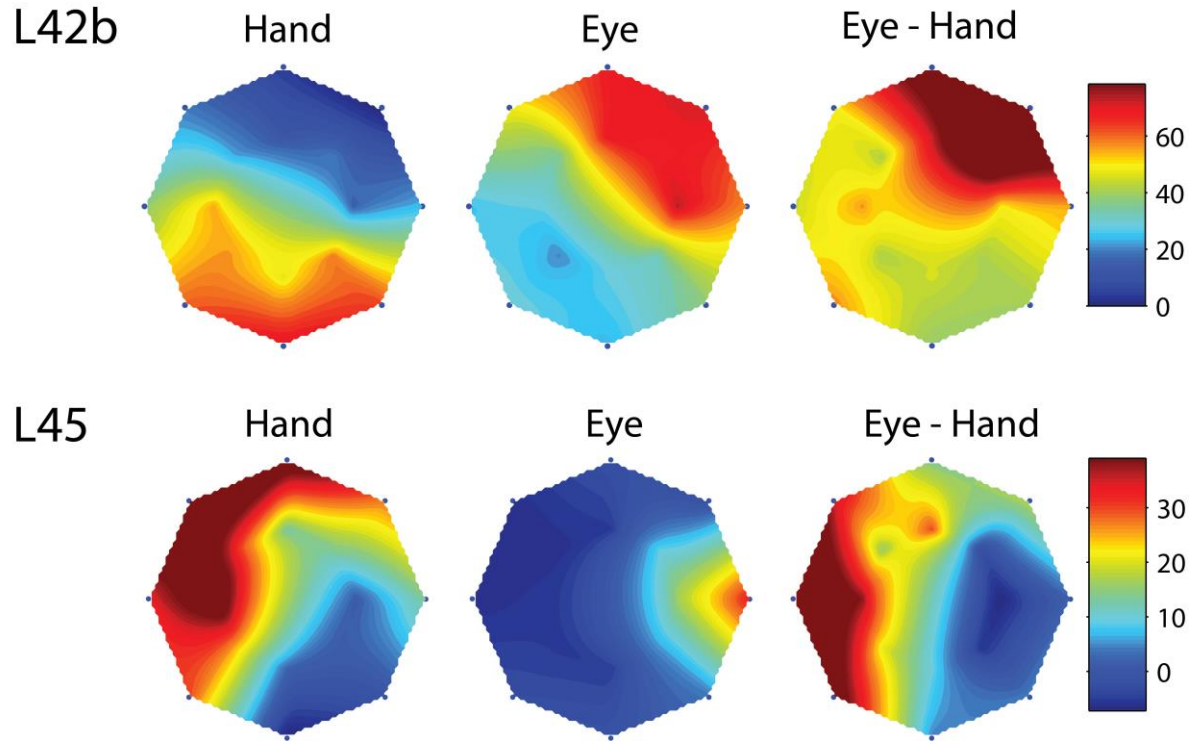

Figure 6. Examples of movement fields of neurons that prefer one direction for saccades and another for hand movements. The color scale on the right is proportional to discharge intensity (spikes/s).

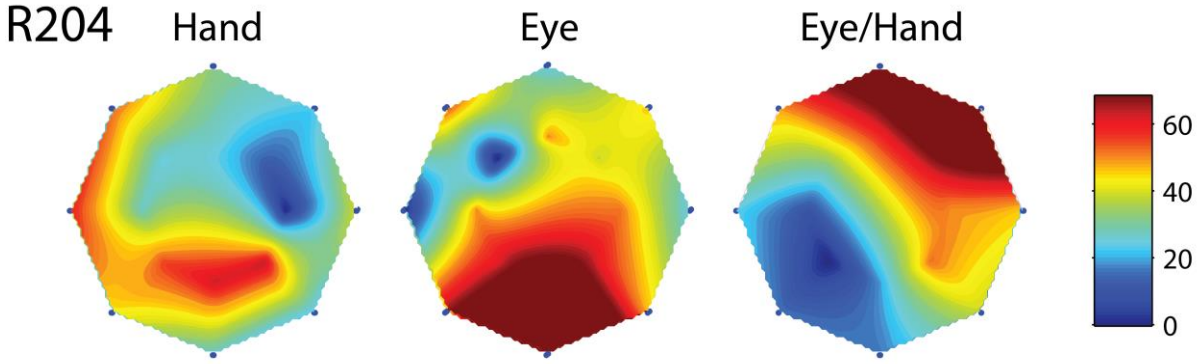

Figure 7. Movement fields of a neuron (R204) whose on-direction for eye-hand movements did not resemble either its on-direction for hand movements or its on-direction for saccades. Layout as in Fig. 6.

Finally, we found two neurons whose movement field changed dynamically during coordinated eye/hand trials gradually shifting from one akin to the movement field of saccades earlier in the trial to one resembling the hand movement field later in the same trial. An example is shown in Fig. 8 which illustrates the 2D surface fits to the mean rate of discharge of cell R216 during the movement epoch in saccade trials (left) and hand movement trials (right). The surface representing the movement field of the neuron was defined as the product of a Gaussian distribution (for amplitude) and a von Mises distribution (for directions). We employed the least-squares method to find the parameters of the surface that best fit the data. As shown in the top part of Fig. 8, the direction of saccades it preferred (downward) clearly differed from that of hand movements (upward). The bottom part of Fig. 8 illustrates the movement field of this neuron for coordinated eye/hand movements during different time slices of 20 ms duration, starting from 30 ms before saccade onset (leftmost movement field of Fig. 8) and ending 120 ms after saccade onset (rightmost movement field). As shown here, the cell starts firing for downward movements (i.e., in the direction preferred by saccades) and ends firing for upward movements (i.e., in the direction preferred by hand movements). Such neurons were marked "mixed" in the "On-direction" column of Table II

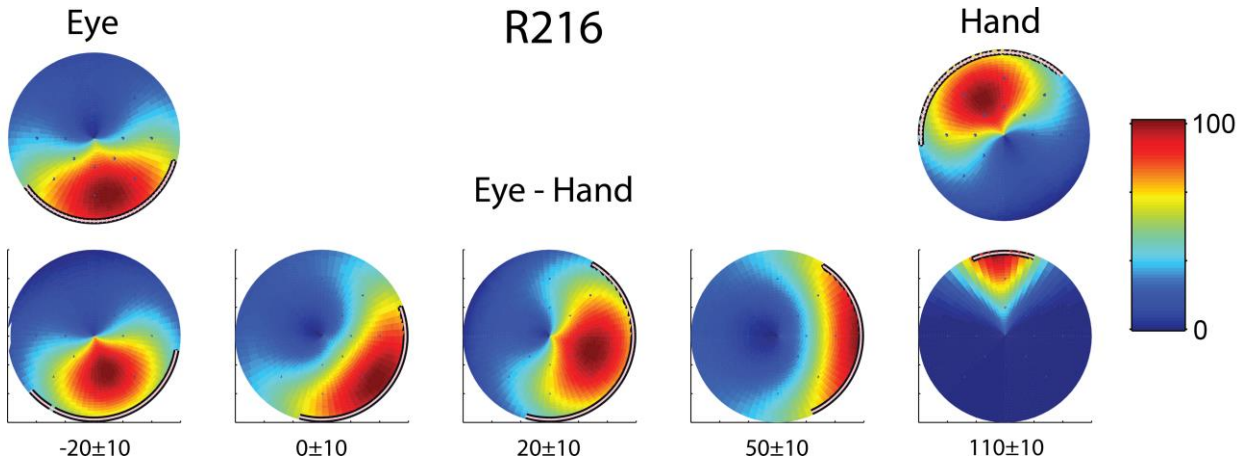

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Figure 8. Example of a neuron (R216) which exhibited dynamic shift of preferred direction during eye/hand movements. The top row displays the fields for single effector (eyes: left; hand: right) movements. The bottom row shows the gradual transition of the movement field for coordinated eye/hand movements. Values at the bottom indicate the onset and offset of the rasters that provided the data for constructing the field in question. The color scale on the right is proportional to the feature scaled intensity of discharge (zero minimum intensity, 100 maximum intensity).

The movement fields of Meq neurons were rather wide. They measured 160±62° (mean±SD) for saccades and 162±65° for hand movements as determined from the $2/\sqrt{k}$ parameter of the von Mises distribution fitted to them. To obtain an intuitive feeling of their size it is instructive to compare them to the size of the movement field of M1 neurons described by Amirikian and Georgopoulos (2000). The median half-width of 30 M1 cells with symmetric profiles equaled 56° and would obtain a value of 90° for a truly sinusoidal field. Instead the $2/\sqrt{k}$ parameter of a truly sinusoidal field would equal 117° if one were to fit it with the von Mises distribution. Cells with wide movement fields for saccades did not always display wide movement fields for hand movements and the same was true for cells with narrow movement fields (Fig. 9). In fact, the width of the saccade related movement field of 25 Meq neurons was significantly different (Fig. 9C, solid) from that of the hand related movement field of the same cells ($p<0.05$, Bartlett's test).

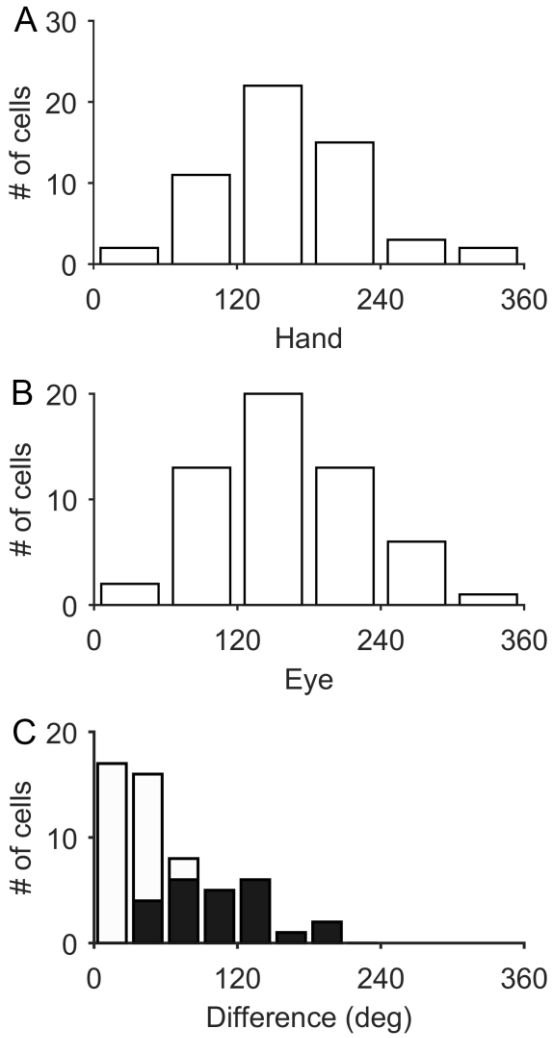


Figure 9. Distribution of field widths for hand (A) and eye movements (B). (C) Frequency histogram of their differences. Black bars indicate statistically significant values.

To examine if Meq neurons show a preference for eye or hand movements in terms of firing rate, we measured their mean rate of discharge during the half-width of their phasic discharge, defined as the time period between the first rise of the instantaneous firing rate function to values higher than $\frac{\text{peak rate} - \text{baseline rate}}{2}$ and the first drop below this value. It could be as low as 18 spikes/s or as high as 166 spikes/s for movements in their preferred direction depending on the neuron and the effector employed. In general, the higher a neuron's rate of discharge for saccades (R_E) the stronger its rate of discharge for hand movements (R_H, Fig. 10A). The two variables were related through the expression $R_E = 18+0.73R_H$ ($R=0.59$, $p<0.001$). The regression of the intensity of discharge for eye-hand movements (R_{EH}) onto R_E and R_H (Fig. 10A, inset) was even stronger ($R_{EH} = 11.3+0.45R_E +0.57R_H$; $R=0.81$, $p<0.001$). The eye movement discharges of the majority (39/55) of the Meq cells we studied did not differ significantly from those for hand movements. Such cells lie close to the diagonal and are marked as solid circles in Fig. 10A. They are also marked as "same" in the "intensity" column of Table II. Sixteen neurons displayed significantly stronger discharges ($p<0.05$, t-test) for one of the effectors (half for the eye and the remaining 8 for the hand). In six of them, the discharges during coordinated eye-hand movements were statistically indistinguishable from those during single effector saccades while they were indistinguishable from single effector hand movements in another 8 cells. The intensity of the discharge for eye-hand movements of the remaining 2 neurons (marked intermediate in the "intensity" column of Table II) did not differ significantly from that during either saccades or hand movements.

The intensity of Meq neuron discharges might be related to a movement related physical variable such as effector velocity. To see if this was the case we plotted peak firing rate during individual trials versus peak effector velocity for movements of the same amplitude in the preferred direction and the two neighboring ones after subtracting the reference discharge. Figure 10 (B, C) shows two examples of the good relationship between neuron discharge and movement kinematics. Figure 10B illustrates a neuron (L42a4) whose peak firing rate was significantly related ($p<0.05$) to peak eye velocity while Fig. 10C illustrates a cell (L53) whose peak firing rate was significantly related ($p<0.001$) to peak hand velocity. Such relationships were rare;

peak discharge was significantly correlated to eye velocity in 5 cells, to hand velocity in 7 cells while it was related to both eye and hand velocity in 2 cells.

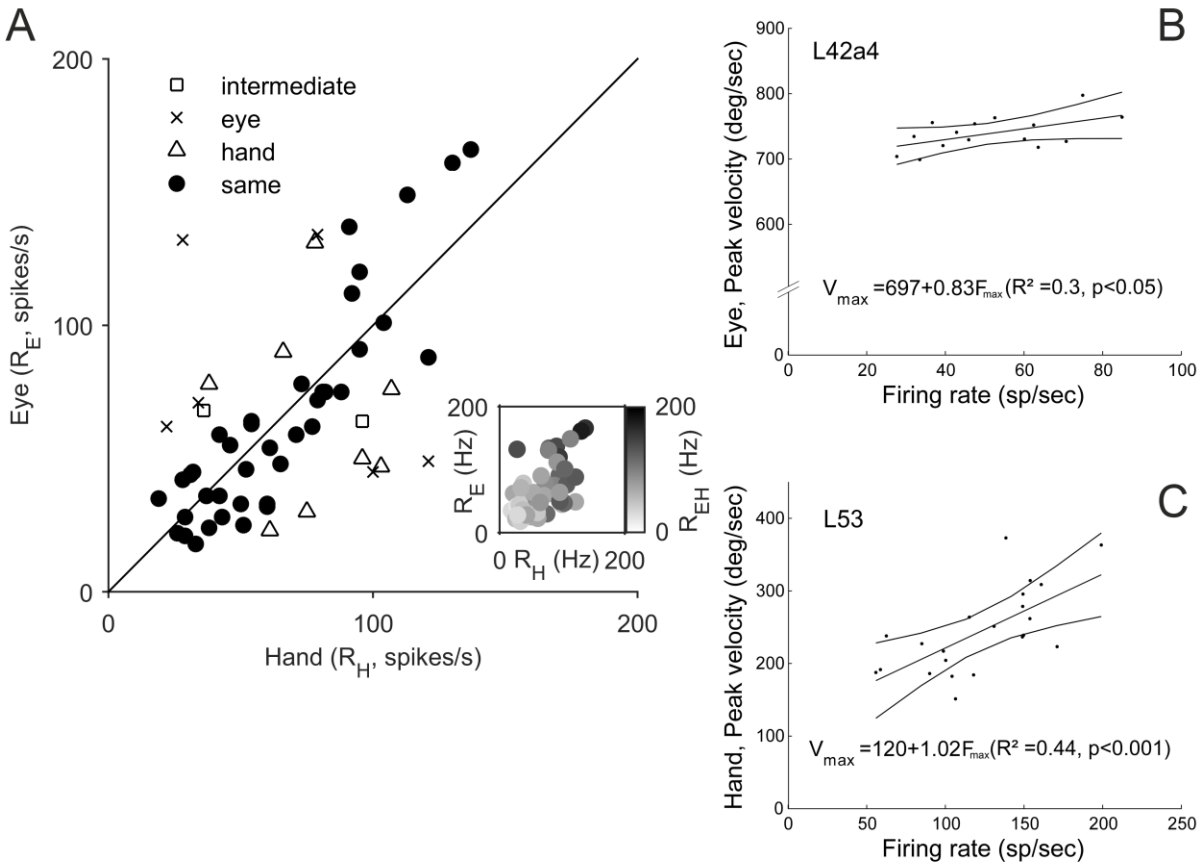


Figure 10. (A) Scatter plot of the relationship of Meq neuron rate of discharge for hand movements (R_H, abscissa) versus rate of discharge for eye movements (R_E, ordinate). Each data point is from a different neuron. The straight line is the unity line. Solid circles indicate neurons with similar discharges for eye and hand movements (p>0.05, t-test). The inset uses a gray scale to illustrate the relationship between the rate of discharge for coordinated eye-hand movements (EH) and Eye (E) as well as Hand (H) movements. (B, C) Examples of the relationship between peak effector velocity (ordinate) and peak discharge rate (abscissa) for two Meq neurons. Lines indicate the linear regression lines (straight), obeying the expressions displayed, and the 95% confidence intervals.

Since there was an almost five-fold difference between the duration of saccades (10°: 45 ms, 20°: 58 ms) and hand movements (10°: 198 ms, 20°: 257 ms) we decided to examine if the duration of the discharge of Meq neurons for saccades differs from that for hand movements. To this end we measured the half-width of the movement related discharge as defined above. Targets eliciting movements not

accompanied by statistically significant (unpaired t-test) discharges (relative to the reference discharge) were discarded. An indication of discharge duration is obtained from the mean value of the half-widths of all movements to retained targets. As shown in Fig. 11, the duration of the discharge of several Meq neurons was equally short or long for hand movements and saccades. These cells (32/55) lie close to the diagonal and are marked as solid circles in Fig. 11. They are also marked as "same" in the "duration" column of Table II. Several other neurons (N=23) did not behave in this manner. With three exceptions (the two x and one open triangle to the left of the diagonal) these exhibited short discharges for saccades and prolonged discharges for hand movements. Given the fact that the difference is worth several hundreds of milliseconds it is meaningful to ask if the duration of the discharge of such a neuron would be short (i.e., saccade like) or long (i.e., hand like) when neuron discharges accompany coordinated movements of the eyes and hand. Figure 12 shows two examples. The top one (cell L53) displayed long discharges for hand movements and short discharges for saccades and also displayed short discharges during coordinated eye/hand movements. Twelve of the Meq cells we encountered discharged in a similar manner and are marked "eye" in the duration column of Table II. This contrasts the discharge of cell R354 (Fig. 12, bottom) which also displayed long discharges for hand movements and short discharges for saccades, but emitted bursts of fairly long duration for coordinated eye/hand movements. A total of 5 neurons discharged in a similar manner (marked "hand" in the duration column of Table II), while the duration of the discharge of 3 cells for eye/hand movements was intermediate relative to that for saccades and hand movements.

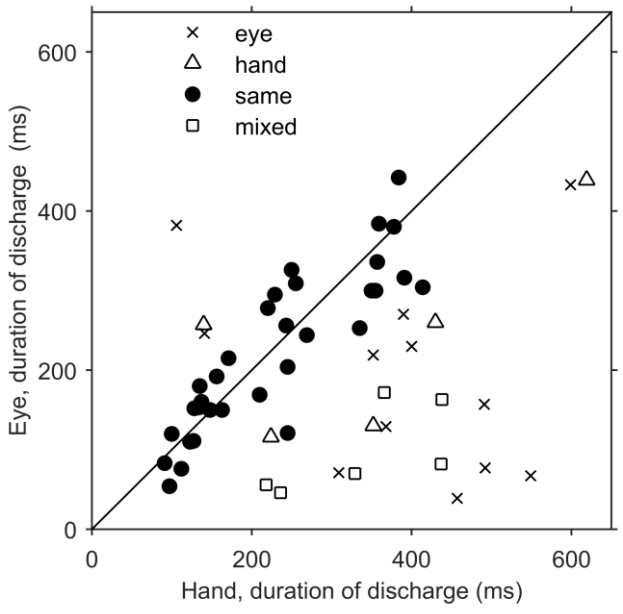


Figure 11. Scatterplot of the average duration of discharge of Meq neurons in trials when the monkey had to move their hands alone (abscissa) versus the average duration of discharge of the same neurons in saccade trials (ordinate). Each point is from a different neuron. Solid circles indicate neurons with similar durations of discharge for eye and hand movements (p>0.05, t-test).

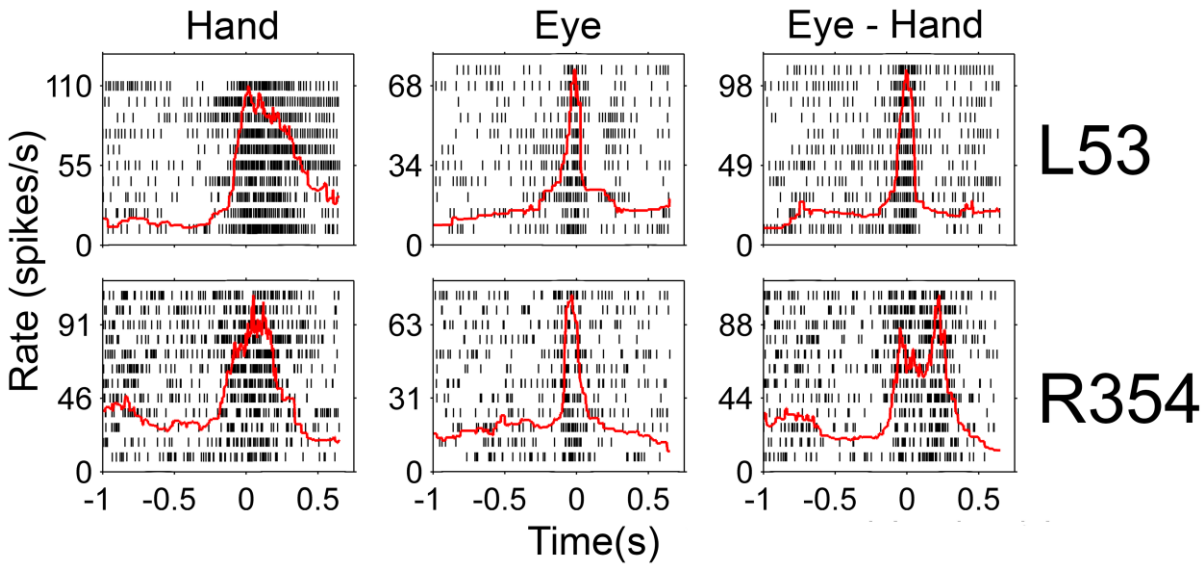


Figure 12. Examples of neurons whose duration of discharge was not the same for eye and hand movements. Red lines indicate the instantaneous firing rate and are aligned on movement onset as are the rasters.

Figure 13 illustrates a somewhat more complex discharge pattern that we observed very infrequently (N=3). As with the neurons described in the previous paragraph, this cell (L76) displayed long discharges for hand movements and short discharges for saccades. It is important to note that the preferred direction of this neuron also differed depending on the effector that was to be moved. It was 265° (i.e., downward) for saccades and 41° (i.e., rightward) for hand movements. In turn, the duration of the discharge of cell L76 for coordinated eye/hand movements depended on the direction of the movement. It was short for downward eye/hand movements (i.e, movements in the direction preferred by the eyes) and long for rightward eye/hand movements (i.e, movements in the direction preferred by the hand). Cells such as this are marked "mixed" in the Duration column of Table II.

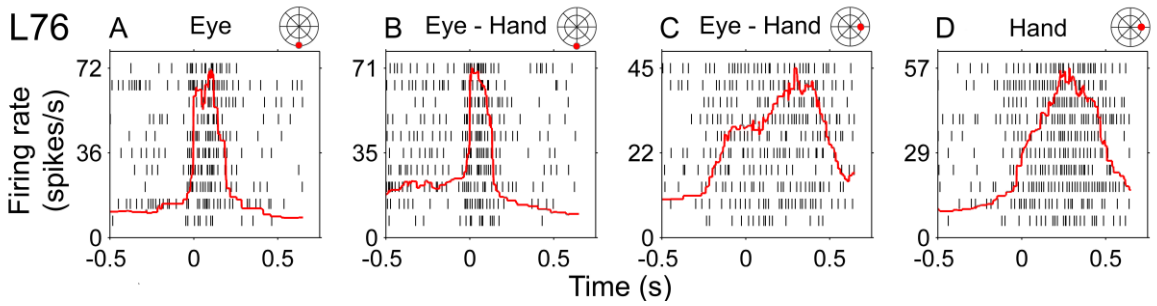


Figure 13. Example of neuron (L76) whose duration of discharge for coordinated eye-hand movements could be either short (saccade-like) or long (hand-like) depending on the direction of the eye-hand movement. The two leftmost rasters are from downward movements (shown by the red solid circle on the cartoon of directions and amplitudes) and are aligned onto saccade onset. The two rightmost rasters are from rightward movements and are aligned onto hand movement onset

In most of the coordinated eye/hand movements we examined, saccade onset preceded the onset of hand movements by 81±33 ms (mean±SD; range: -41 - 148 ms). Accordingly, it was not surprising to see that the discharge of Meq cells led the onset of hand movements by 152±51 ms (mean±SD; range: 40-294 Fig. 14A) but led the onset of saccades by only by 70±41 ms (mean±SD; range: 6-191 Fig. 14B). To further assess the temporal relationship between the onset of the discharge of Meq neurons and the onset of effector movement, we measured the latency of the discharge in individual eye/hand trials. If the discharges of Meq neurons determine the onset of movements of the eyes and/or the hand one would expect the earlier or later onset of their discharge to be translated into the earlier or later onset of the movement of the effector they influence. To examine if this is the case for one or both of the effectors, on a trial by trial basis, we aligned all rasters accompanying coordinated eye-hand movements within 45° of the cell's on-direction on the onset of one of the effectors, and examined the correlation between the onset of the discharge and the onset of the movement of the other effector. We defined the onset of the discharge in each trial separately as the point in time when the instantaneous firing rate exceeded the reference discharge by 2 SD (see Methods for further details).

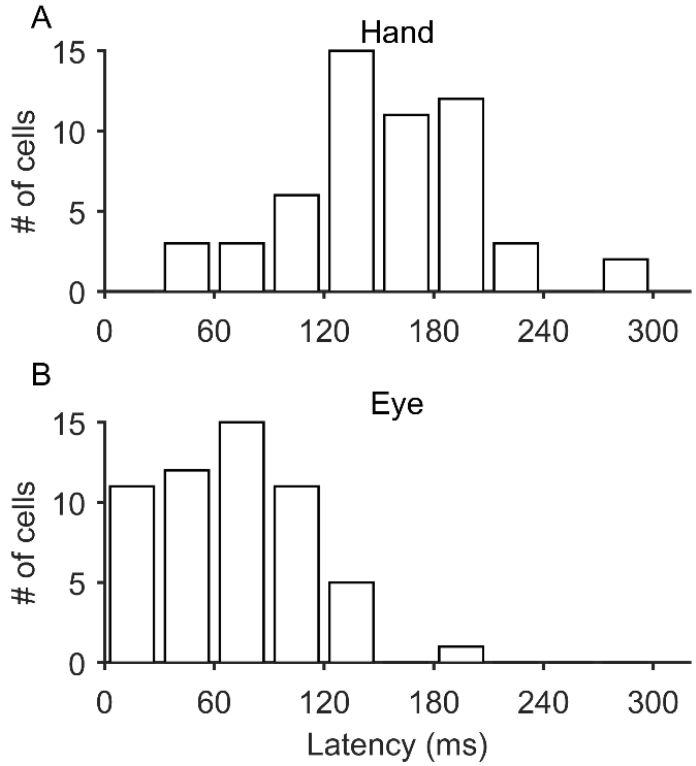


Figure 14. Frequency histogram of the distribution of latencies of Meq neurons relative to the onset of hand movements (A) and saccades (B).

The top row of Fig. 15 shows a neuron (R211) whose discharge onset is significantly correlated with the onset of both saccades and hand movements ($p<0.002$ & $p<0.001$ respectively). Figure 15B is a scatter plot of the onset of hand movements versus discharge onset for trials aligned on the onset of saccades. The linear model accounted for a sizable proportion of the variance (41%) of the dependent variable. A statistically significant relationship ($p<0.002$), albeit weaker ($R^2=0.26$), was also found between the onset of the discharge and the onset of the saccades when the trials were instead aligned on the onset of the hand movement (Fig. 15C). The onset of the discharge of another 9 Meq neurons displayed similarly good correlations with the onset of the movement of both effectors (R^2=7-41% for hand movements and 8-53% for saccades). Cells such as these are marked "both" in the "Onset" column of Table II.

Figure 15G is a scatter plot of the onset of saccades versus discharge onset for trials aligned on the onset of hand movements within 45^o of the on direction of cell L52b. The correlation coefficient (0.79) indicates that most of the variance of the dependent variable is accounted for ($p<0.001$). In this case, aligning the eye-hand trials on saccade onset did not result in a linear relationship between the onset of the hand

movement and the onset of the discharge of this cell (Fig. 13F). Surprisingly, the majority of Meq neurons in our sample (N=36) displayed such good correlations with the onset of saccades (R^2=12-88%) and not the onset of hand movements. One might argue that alignment on the onset of the movement of an effector that is almost perfectly correlated with discharge onset (as is the case in Fig. 15G for saccades) would result in the almost perfect alignment of the independent variable as well (in this case the onset of the discharge) and thus its correlation with the onset of the movement of the other effector might be poor because the range of values of the independent variable has been restricted excessively. To address this issue, we examined the relationship between discharge onset and movement onset in single effector trials in which the subject was rewarded for moving the hand and not the eye after aligning the trials on the GO signal. Twenty one of the 36 seemingly eye related Meq cells in our sample displayed a statistically significant correlations between discharge onset and hand movement onset (R^2=9-55%) in such single effector trials and are also marked "both" in the "Onset" column of Table II. The onset of the discharge of the remaining 15 Meq cells remained insensitive to the onset of the hand movement even in single effector hand trials; such cells are marked "eye" in the "Onset" column of Table II.

Finally, the onset of the discharge of some Meq neurons was correlated with the onset of hand movements rather than the onset of saccades. The bottom row of Fig. 15 provides an example. Figure 15J is a scatter plot of the onset of hand movements within 45° of the on-direction of cell L84 versus the onset of its discharges for trials aligned on the onset of saccades. Much of the variance of hand movement onset (R^2=46%) is accounted for by the jitter of discharge onset ($p<0.001$). In the case of neuron L84, aligning the eye-hand trials on the onset of hand movements did not result in a linear relationship between saccade onset and discharge onset (Fig. 15K). The discharge of another 8 Meq neurons displayed similar relationships to the onset of effector movement. For reasons outlined in the previous paragraph, in these cases we also examined the relationship between discharge onset and saccade onset in single effector saccade trials after aligning the trials on the GO signal. Five of the 9 seemingly hand related Meq cells displayed statistically significant correlations between the onset of the discharge and the onset of saccades (R^2=11-36%) in such single effector trials and are also marked "both" in the "Onset" column of Table II. The onset of the discharge of the remaining 4 cells remained insensitive to the onset of the saccades in single effector trials and are marked "hand" in the "Onset" column

of Table II. To summarize, the onset of the discharge of the majority of Meq neurons seems better correlated to the onset of saccades than the onset of hand movements.

To assure ourselves that this is the case, we aligned all trials within 45° of a Meq cell's on-direction on the onset of its discharge and constructed the frequency histograms of the latencies of the effector movements they accompany. If the onset of the discharge is better related with the onset of saccades one would expect the frequency histogram of the latency of hand movements to be wider than that of saccades. The opposite would be true if the onset of the discharge was better related to the onset of hand movements. Figs. 15I and 15L are the frequency histograms of the latency of the onset of relevant hand movements and saccades, respectively, which accompany the discharge of neuron L84. The SD is 41 ms for saccade latencies (SD_E) and 56 ms for hand latencies (SD_H) again demonstrating that this neuron's discharge is better aligned to the onset of the eye rather than that of the hand movement. For each of the Meq cells we calculated the ratio of SD_E/SD_H. It was smaller than one (range: 0.31 to 0.97) in the 36 Meq cells better related to saccade onset as determined from the jitter analysis described above. For example, the spread of saccade latencies was 3.2 times smaller than that of hand latencies, a highly significant difference ($p<0.0002$; Bartlett's test), in neuron R238 which occupies one end of this range. The smaller spread of saccade latencies proved statistically significant in 28 of these 36 Meq cells using either Bartlett's ($p<0.05\text{-}10^{-9}$) and/or the Kepner-Randles test ($p<0.05$; see Methods for a short description of this statistic). Conversely, it exceeded one by only 9% - 34% in the 9 Meq cells better related to hand onset, as determined from the jitter analysis, but these differences did not prove statistically significant. This analysis reinforces our conclusion that the onset of the discharge of Meq cells is better correlated to the onset of saccades than the onset of hand movements.

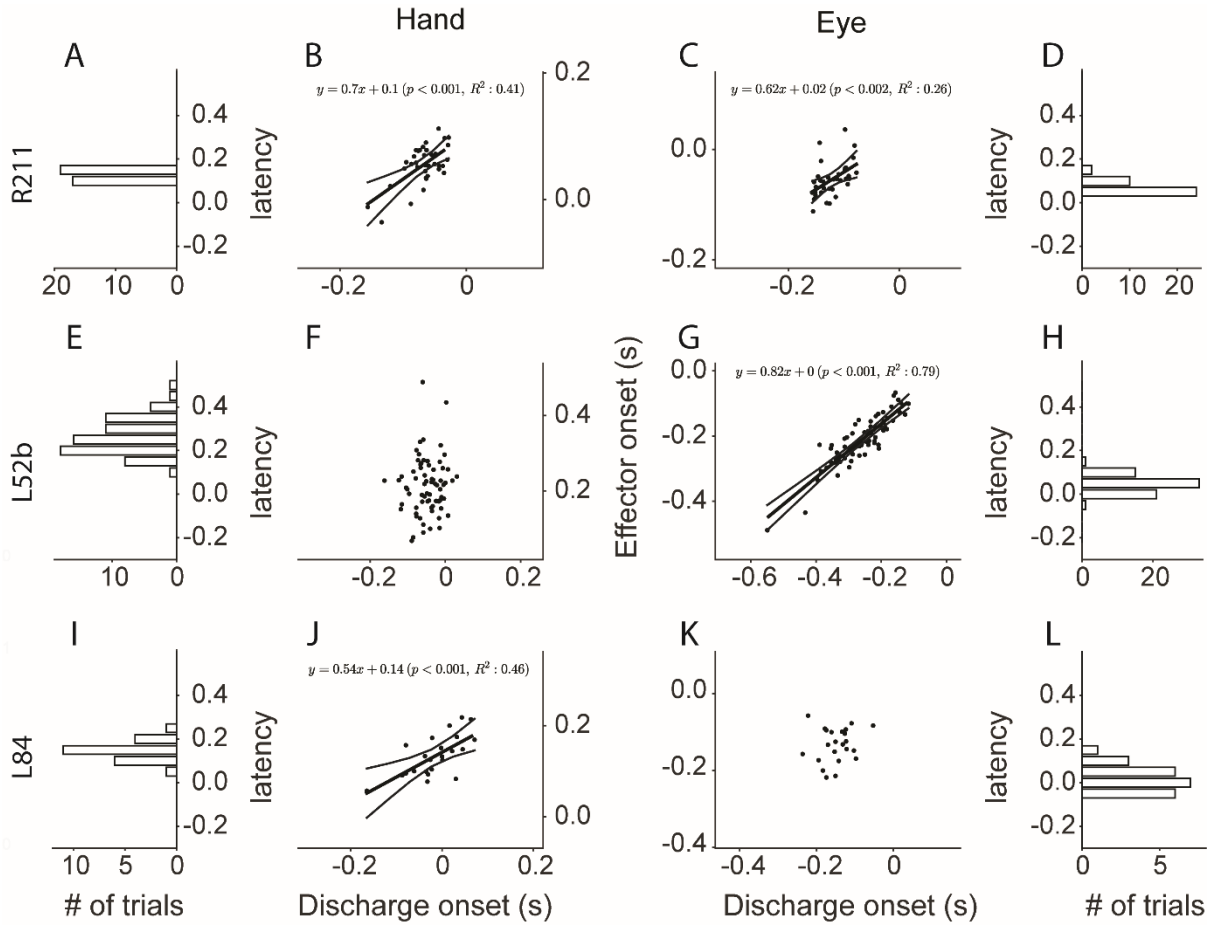


Figure 15. Scatter plots of the onset of the discharge of Meq neurons (abscissa) versus the onset of Hand movements (ordinate in B, F, J) and saccades (ordinate in C, G, K) in coordinated eye hand movements. Each point is from a different trial. Lines indicate the linear regression lines (straight), obeying the expression displayed, and the 95% confidence intervals. The frequency histograms show the distribution of the latencies of discharge (behavior onset minus discharge onset, in seconds) relative to the onset of the hand movement (A, E, I) or the saccade (D, H, L).

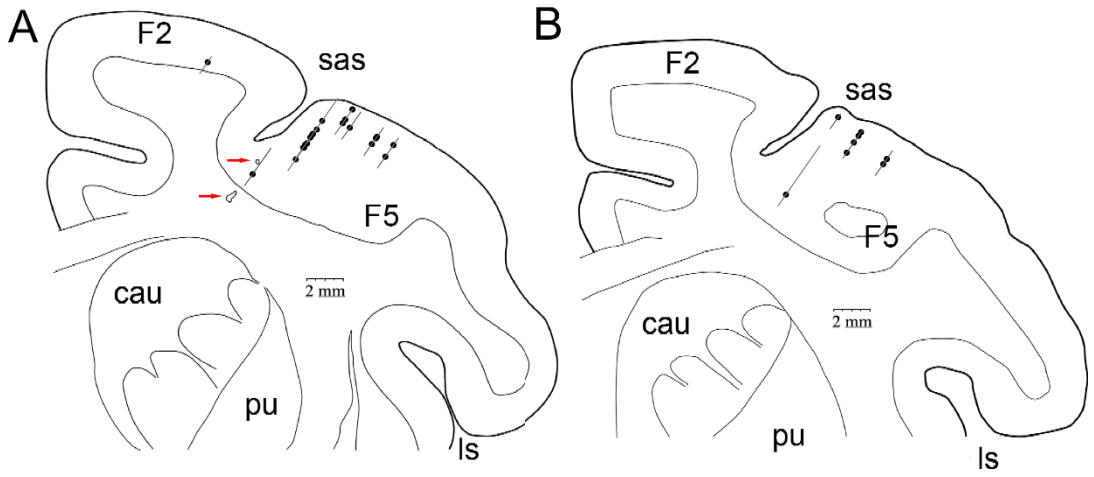
Cell ID	On-direction	Intensity	Duration	Onset
L36	invariant	eye	same	both
L42A1	hand	hand	same	both
L42A4	***mixed***	hand	same	both
L42b	eye	same	same	both
L45	hand	same	same	both
L47	invariant	same	same	both
L52b	invariant	same	eye	eye
L53	invariant	same	eye	both
L56	***mixed***	same	same	eye
L61	***intermediate***	same	same	eye
L62	***intermediate***	same	same	both
L63	hand	same	eye	hand
L76	hand	same	***mixed***	both
L78	invariant	same	same	both
L79	invariant	eye	eye	both
L81	hand	same	same	eye
L83	invariant	same	eye	eye
L84	***intermediate***	eye	same	both
L87	invariant	same	same	both
L88b	hand	same	hand	eye
L89	invariant	same	same	both
L91	invariant	same	eye	both
L94	***intermediate***	hand	same	eye
L96	invariant	same	***intermediate***	both
L97	eye	eye	same	hand
L98	invariant	same	***mixed***	both
L100	invariant	same	same	eye
R2	invariant	same	same	both

Cell ID	On-direction	Intensity	Duration	Onset
R37	invariant	same	same	both
R50	invariant	same	same	both
R62	eye	hand	hand	both
R202	***mixed***	same	eye	eye
R204	***intermediate***	***intermediate***	hand	eye
R211	eye	eye	eye	both
R216	***mixed***	same	***mixed***	both
R222	invariant	same	eye	both
R224	***intermediate***	hand	same	both
R233	hand	same	same	hand
R234	eye	same	same	both
R238	hand	same	same	eye
R239	invariant	same	same	eye
R244	eye	same	***intermediate***	both
R248	invariant	hand	same	both
R249	invariant	hand	same	both
R250	invariant	same	eye	both
R251	invariant	hand	invariant	both
R333	eye	same	***intermediate***	both
R337	invariant	eye	eye	both
R338	eye	same	same	eye
R340	eye	same	eye	eye
R352	eye	same	same	both
R353	invariant	same	hand	both
R354	invariant	same	hand	eye
R357	invariant	same	same	both
R358	invariant	same	same	hand

Table II. Classification of Meq cells according to the effector they prefer (eye: dark, hand: gray)

Figure 16 illustrates the number of the Meq neurons we found in different parts of the periarcuate cortex, shown as solid circles the diameter of which is proportional to the number of the Meq cells encountered within 1 mm of its center, juxtaposed to the total number of neurons encountered in the same region (gray circles). Figure 16A illustrates portions of tracks found within 500 microns of the illustrated frontal section which passed 22 mm in front of the interaural line of subject R. A second section one mm rostral the first is also illustrated (Fig. 16B). Besides placing small electrolytic lesions (Fig. 16A, red arrows) we anchored our observations on the medial and caudal borders of area F5 (Fig. 16C, hatched) which was mapped with the help of single cell recording for the needs of an experiment focusing on mirror neurons and in which our subjects also participated. They were also anchored on the borders of the smooth pursuit area (Fig. 16C, green lines) that were mapped in this as well as subject L with the help of electrical microstimulation. As shown in Fig. 16C, the majority of the Meq neurons in our sample were found in or near the mirror neuron

and the smooth pursuit region of the caudal bank of the AS (N=41). We also wished to examine if there are Meq cells outside this relatively restricted area of the AS. We were able to find them more caudally in the premotor cortex, 8 dorsal and another 3 ventral to the spur, while 2 were found intermingled with FEF cells in front of the AS.



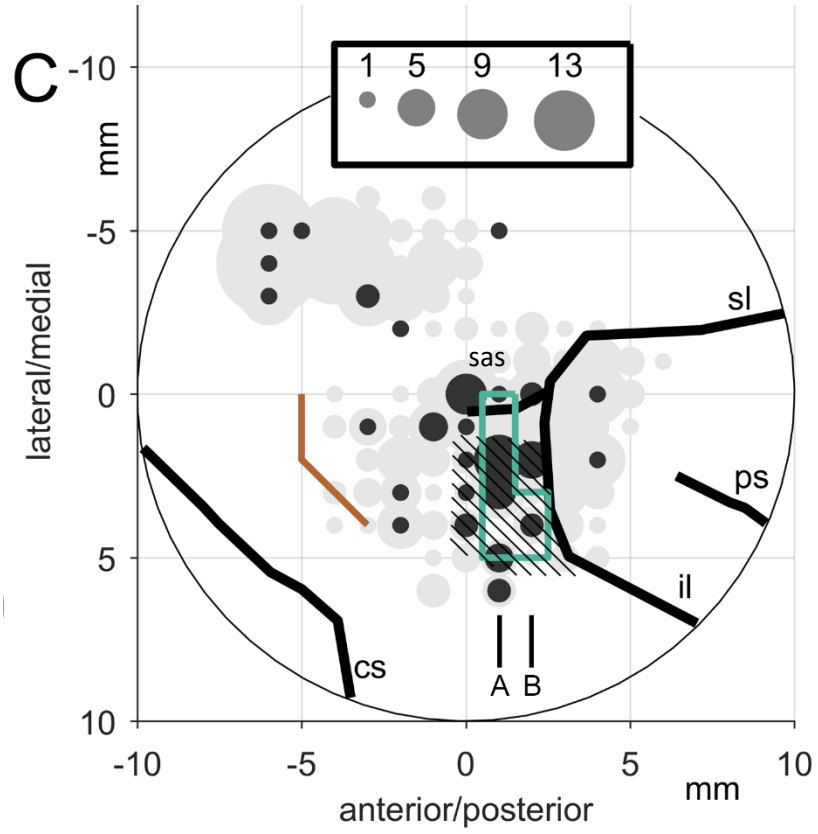


Figure 16. (A, B) Frontal sections through the right premotor cortex of subject R. Their relative location is indicated in C. (C) Location of Meq cells found in the primate periarcuate cortex arranged on a grid centered on the middle of our recording chamber. The area of the discs is proportional to the number of Meq neurons (black discs) or the total number of neurons (gray discs) encountered within 0.5 mm of their center. Data are from 3 hemispheres aligned relative to the smooth pursuit area (enclosed by green lines), area F5 (hatched) and the border between M1 and the premotor cortex (orange). Red arrows point to electrolytic lesions placed in subject R just prior to perfusion to anchor the relative location of electrode tracks. Abbreviations: cs, central sulcus; il, inferior limb of the arcuate sulcus; ps, principal sulcus; sl, superior limb of the arcuate sulcus;sas, spur of the arcuate sulcus.

Saccade related neurons (S)

We found 31 neurons in the premotor cortex that discharged vigorously before the saccades they preferred, both visually guided and memory guided, whether they were accompanied by hand movements or not. Eighteen of these cells also discharged in response to the appearance of a visual stimulus while the remaining 13 did not. Figure 16 provides an example of the discharge of such a neuron (R359) for visually guided saccades in eight different directions arranged as spokes of a wheel (with 0 being the horizontal contraversive) and two amplitudes (10° and 20°). As shown here, more intense discharges accompanied down-right saccades. To obtain a quantitative measure of its on-direction, the intensity of its discharge (as mean discharge in an epoch starting 30 ms before and ending 30 ms after saccade onset) was fitted to the von Mises distribution, defined as $A\frac{e^{k\cos(x-\mu)}}{2\pi I_o(k)}$, where μ is the neuron's preferred direction, A is a scaling factor and $I_o(k)$ the modified Bessel function of order 0, while k provides a measure of the spread of the movement field. In this manner, the on-direction of cell R359 was found to equal 279° and its movement field was relatively narrow ($2/\sqrt{k}$= 91°).

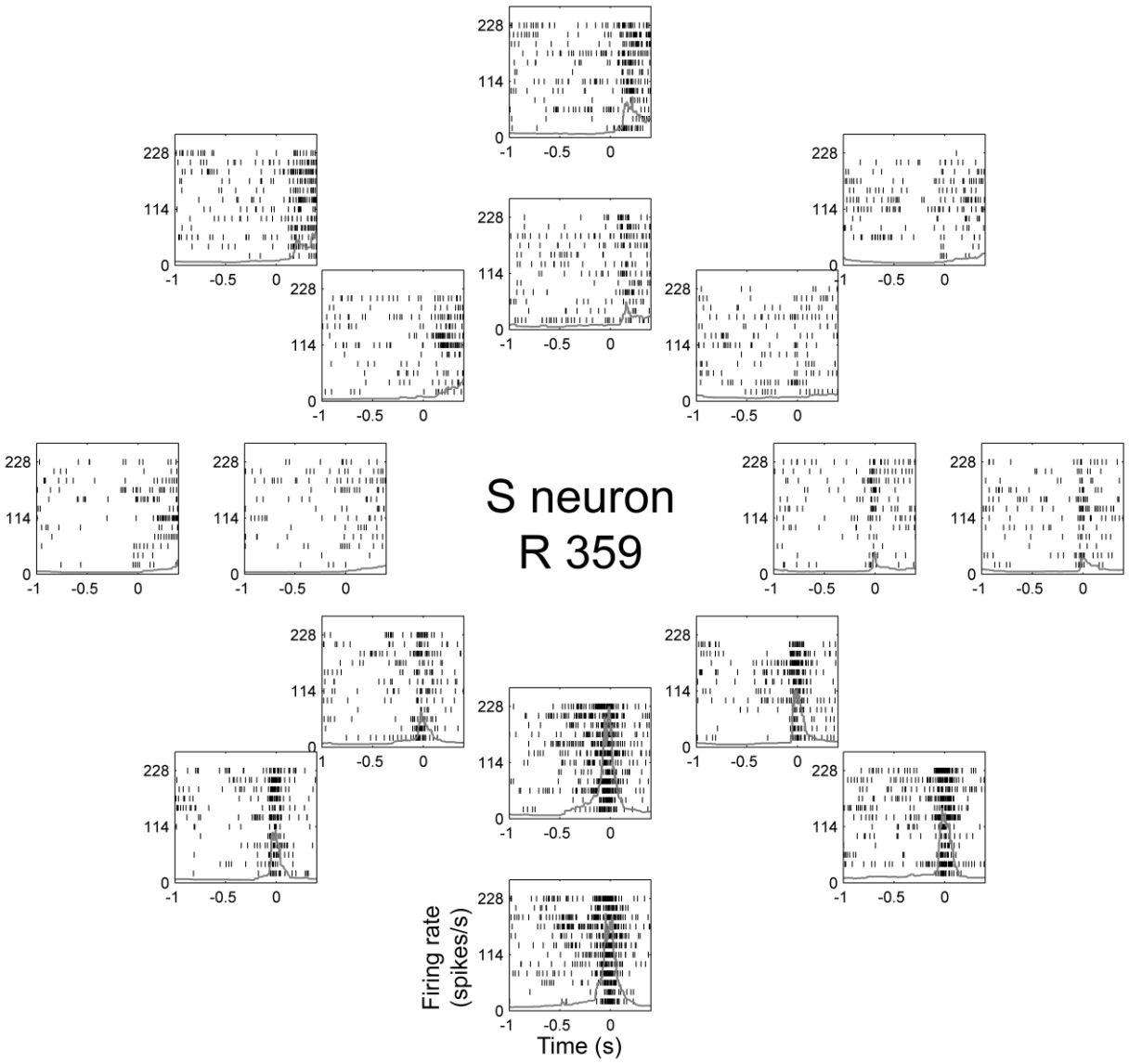


Figure 17. Example of the discharges of an S neuron (R359) of the premotor cortex for saccades in 8 directions and two sizes (10° or 20°). Other conventions as in Fig. 3.

It is instructive to compare the discharge pattern of saccade related cells of the premotor cortex to FEF neurons. To this end we recorded the activity of cells lying in front of the arcuate sulcus (N= 38). Eighteen of these cells also discharged in response to the presentation of visual stimuli and thus correspond to the visuo-movement cells of Bruce and Goldberg (1985); the visual responses of the remaining 20 neurons (movement related cells) were weak or absent. Figure 18 illustrates the example of an FEF neuron that discharged maximally for movements up and to the right (on-direction: 58°) and a somewhat wider movement field ($^{2}/_{\sqrt{k}}$: 144°). We used

the same method to find the on-direction and spread of all S and FEF neurons we studied. Figure 19A compares the distribution of their preferred directions. To examine if S and FEF neurons differ in terms of the lateralization of their on-directions, we counted the number of neurons with ipsiversive and contraversive on-directions after excluding those within 30 deg of the vertical meridian. FEF neurons were more likely to be contraversive (chi-square test, $p<0.05$), while S neurons were as likely to be ipsiversive (N=14) as contraversive (N=17). S neurons also differ from FEF neurons in terms of the width of their fields (Fig. 17B). That of S neurons (average $^{2}/_{\sqrt{k}}$: 135°±66 – mean±SD) is slightly but not significantly bigger ($p=0.07$, Wilcoxon rank sum test) than that of FEF neurons (106°±41, mean±SD). With one exception (FEF neuron R258), the on-direction of neither the S nor the FEF neurons shifted for eye-hand movements relative to that for saccades.

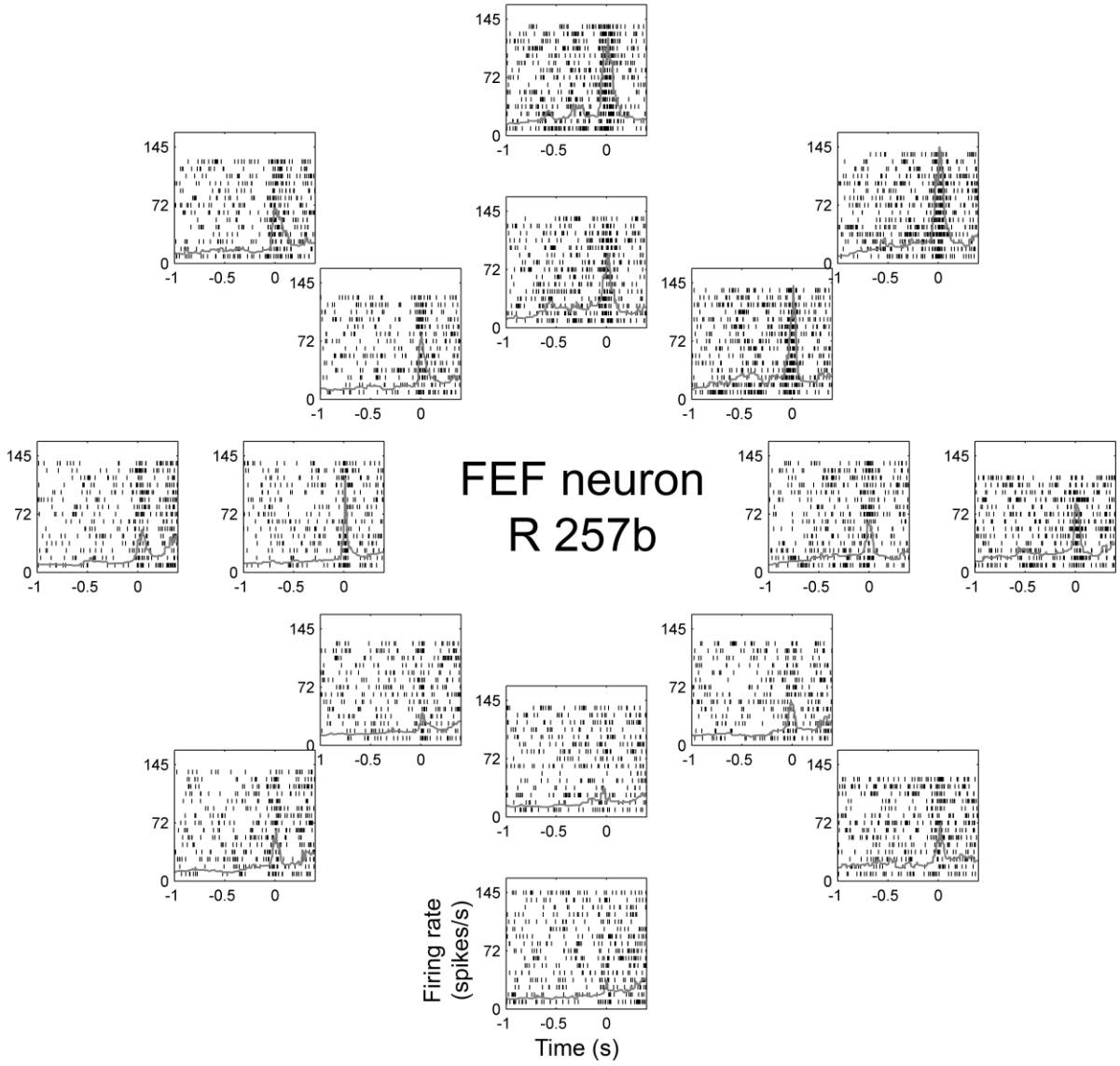


Figure 18. Example of the discharges of a frontal eye field neuron (R257b). Layout and conventions as in Fig. 3.

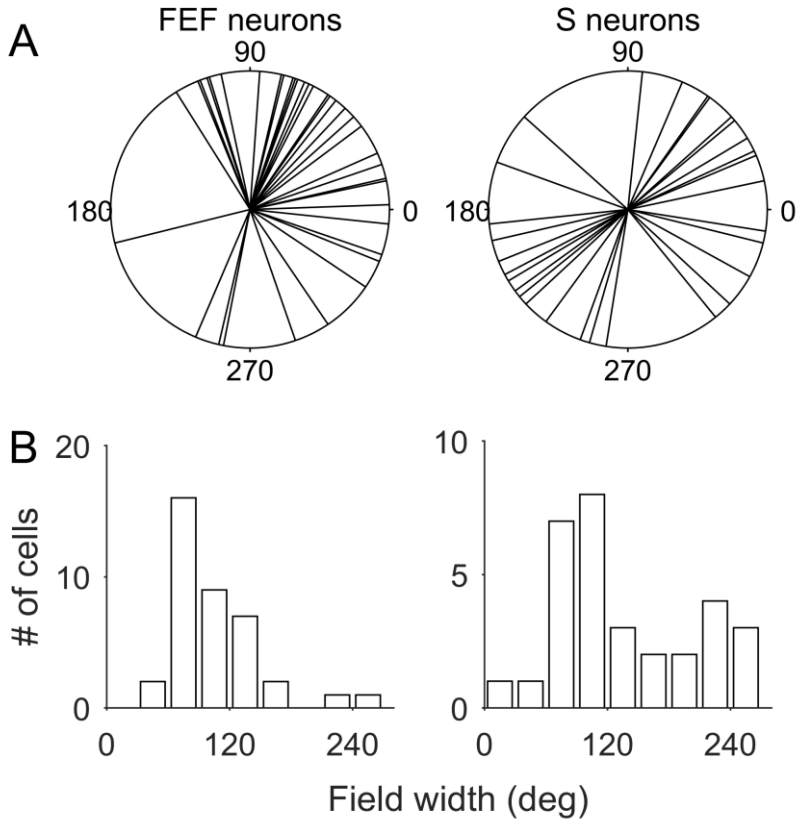


Figure 19. Distribution of the preferred directions (A) and frequency histograms of the field width (B) of FEF neurons (left) and S neurons (right). Zero designates horizontal contraversive movements in (A).

Comparison of Figs. 17 and 18 illustrates a second important difference between FEF and S neurons, namely the duration of their discharge for the saccades they prefer. Those of FEF neurons are brief (mean±SD=100±50 ms) ranging between 34 and 244 ms (Fig. 20A) when measured as the time distance of two points on the instantaneous firing rate curve, the first on its ascending limb halfway between baseline and peak discharge and the second on its descending limb halfway between peak discharge and baseline. The duration of the discharges of S neurons were longer ($p<10^{-3}$, t-test), ranging between 43 and 430 ms (mean±SD=168±100 ms) when measured in the same manner. This fairly extensive range of durations is also illustrated in the examples of the time course of the saccade related discharges of 9

different S neurons shown in Fig. 21. These cells preferred contraversive (R240, R348, L58, L86, R318), upward (R330, R355) or ipsiversive (R336, L99) saccades, respectively. With the exception of L58 (Fig. 21F), these cells displayed a sharp onset and a rather quick rise to peak. Descent to baseline could be equally sharp, as in R330 (Fig. 21C) and L58 (Fig. 21F), or prolonged as in R240 (Fig. 21A) and R318 (Fig. 21I). The peak frequency of their discharges also varied considerably. It could be high, as in R240 (Fig. 21A) and R348 (Fig. 21B) or low as in R330 (Fig. 21C) and R355 (Fig. 21E). To see if, on the average, the intensity of discharge of premotor (S) differs from that of prefrontal (FEF) saccade related neurons we compared the mean rate of the discharges they emitted for saccades in their preferred direction (Fig. 20B). To be consistent, we limited our measurement of firing rate to the time interval we used to estimate the duration of their discharge. When measured in this manner, S neurons were found to emit 67spikes/s on the average (±38, SD) for the saccades they preferred (range: 10-155 spikes/s). The mean firing rate of FEF neurons (mean±SD=77±34 spikes/s; range: 30-144 spikes/s) was not significantly different (t-test, p=0.25). Statistically significant relationships between peak firing rate and peak saccadic velocity were very rare (limited to 3 of the S neurons of our sample).

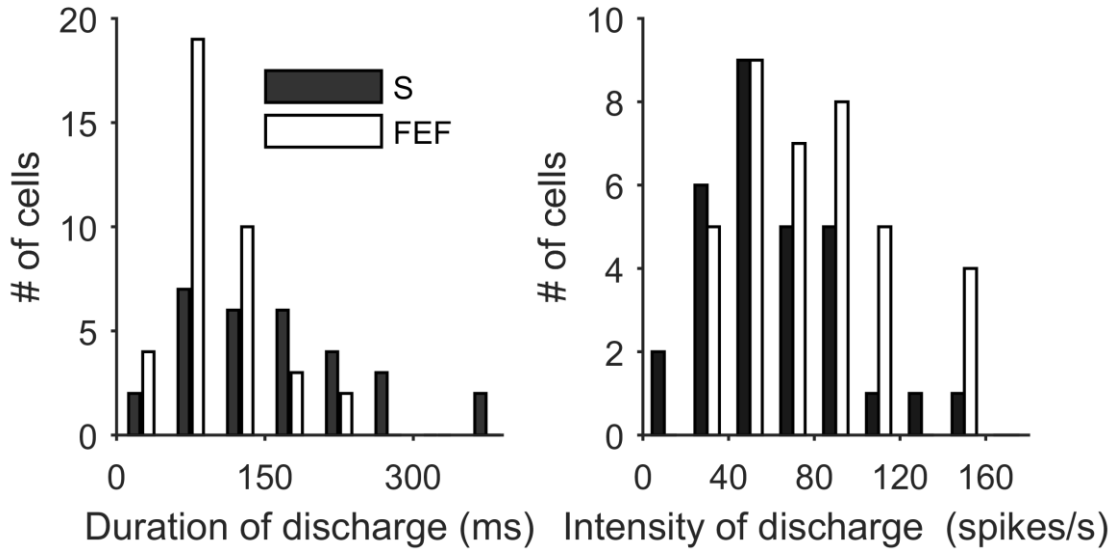


Figure 20. Frequency histograms of the duration (A) and intensity (B) of discharge of FEF (open) and S (solid) neurons.

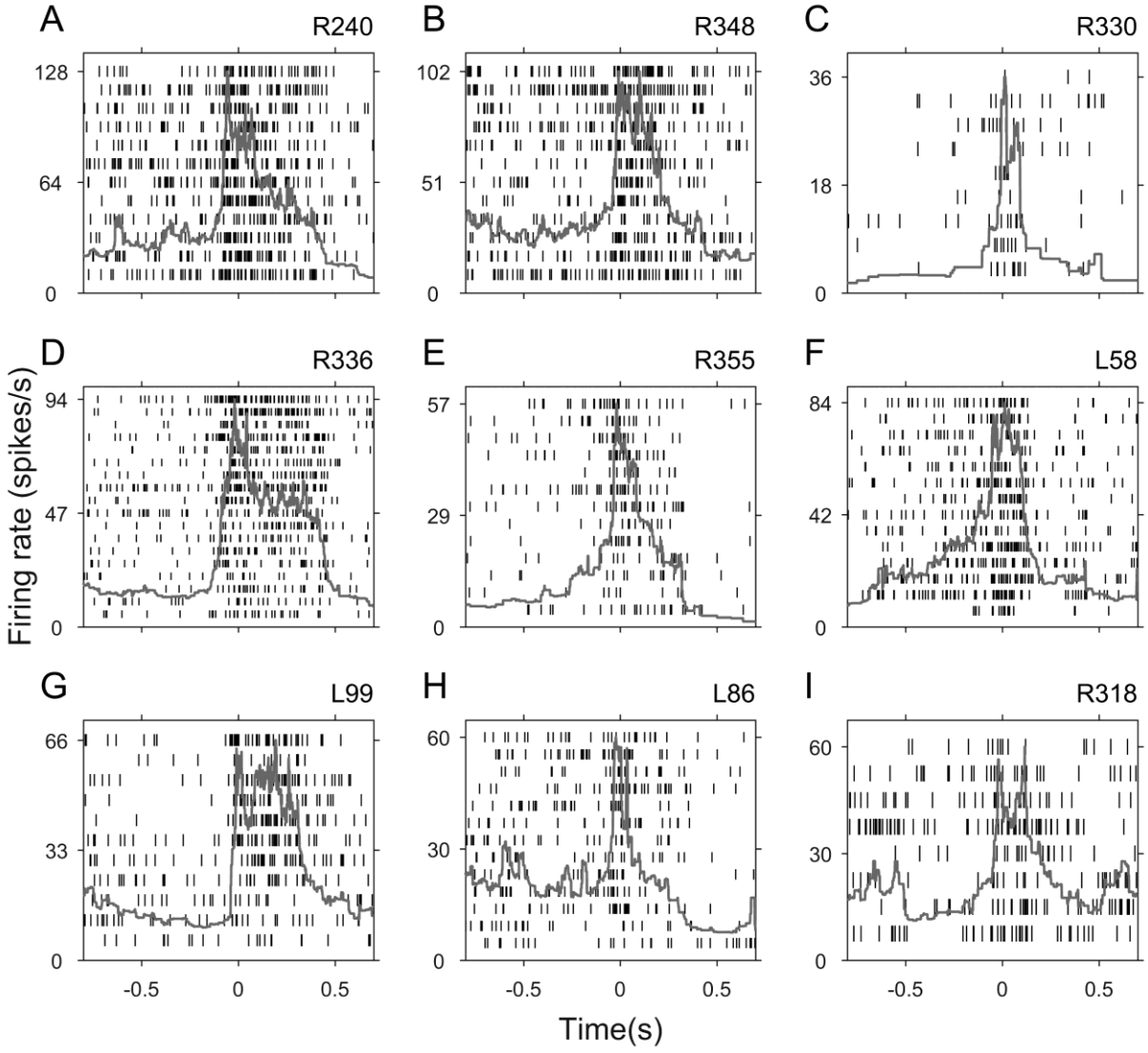


Figure 21. Examples of the discharges of 9 different S neurons aligned on the onset of saccades. Conventions as in Fig. 3.

Figure 22 illustrates another important difference between the saccade related neurons of the premotor cortex (S) on the one hand and the FEF on the other. As a group, the onset of the discharge of S neurons preceded saccade onset by 54±29 ms (mean±SD; range: 10-122 ms), a population average that was significantly longer (t-test $p<5\cdot10^{-3}$) than that of FEF neurons (mean±SD= 33±21 ms). At the same time, the latency of S neurons was significantly shorter (t-test $p<0.05$) than that of Meq neurons (mean±SD= 70±41 ms). We also wanted to explore whether the variability of the onset of the discharge of S neurons was related to the variability of the onset of saccades. To this end, separately for each neuron, we aligned all trials within 45° of a cell's preferred direction onto the onset of the hand movement and explored the linear regression

between discharge onset and saccade onset. Figure 23A provides an example for one S neuron (R287); here, the proportion of the variance accounted for (61%) indicates a fairly strong relationship between S neuron discharge onset and saccade onset ($p<10^{-12}$). The same is true of FEF neurons. Figure 23B provides an example using data from FEF neuron R264. Here again, the onset of its discharges was well correlated ($p<10^{-19}$) to the onset of saccades within 45° of its on-direction (124°) when trials were aligned on the onset of the hand movement (R^2: 0.71). The insets of Figs. 23A and 23B are frequency histograms of the R^2 values found in S and FEF neurons, respectively. With two exceptions, those of S neurons were statistically significant; R^2 ranged from 16 to 83% (p: 0.03-10^{-15}). One of the remaining two cells displayed a statistically significant correlation between the onset of its discharges and the onset of saccades ($p<10^{-5}$) in single effector trials that were aligned on the GO signal and in which the subject was rewarded for moving the eye and not the hand. The frequency histogram for FEF neurons was statistically indistinguishable from that for S cells (p=0.19, two-tailed Wilcoxon). R^2 ranged from 19 to 86% (p: 0.02-10^{-21}) and we failed to find a statistically significant relationship between discharge onset and saccade onset in only 3 FEF neurons. Two of the 3 displayed a statistically significant correlation between discharge onset and saccade onset in single effector trials aligned on the GO signal.

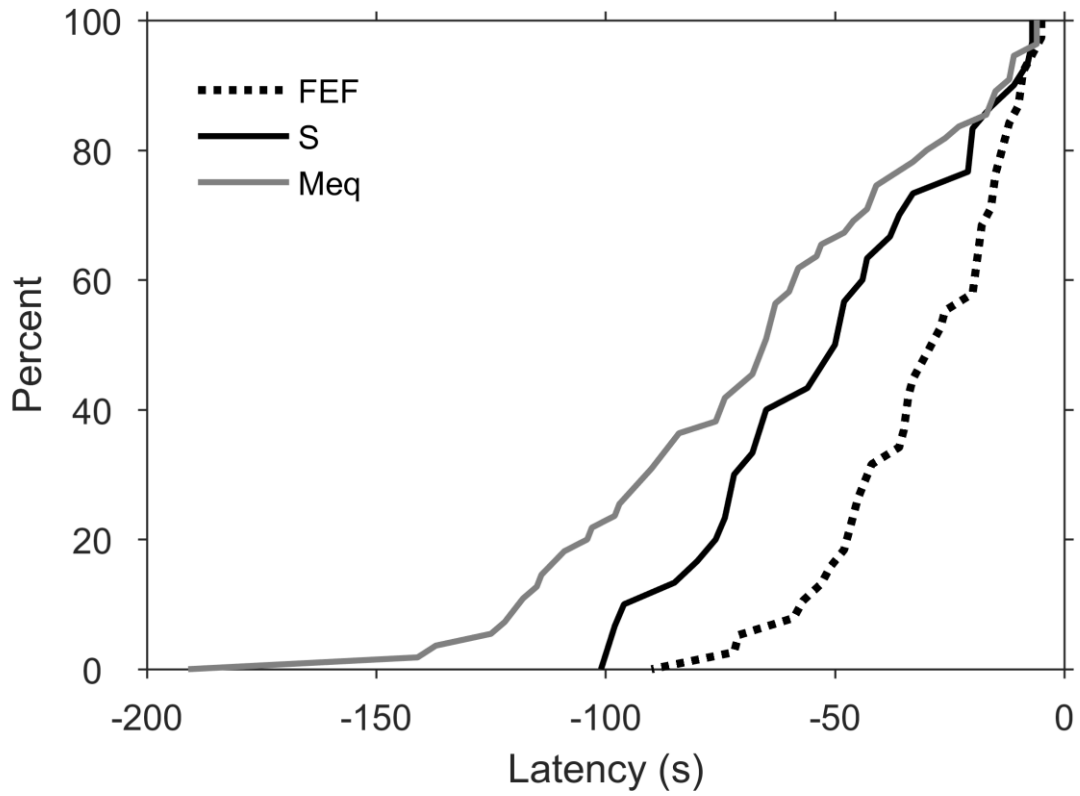


Figure 22. Cumulative frequency histogram of the latency of the Meq (gray), S (solid) and FEF (dashed) neurons.

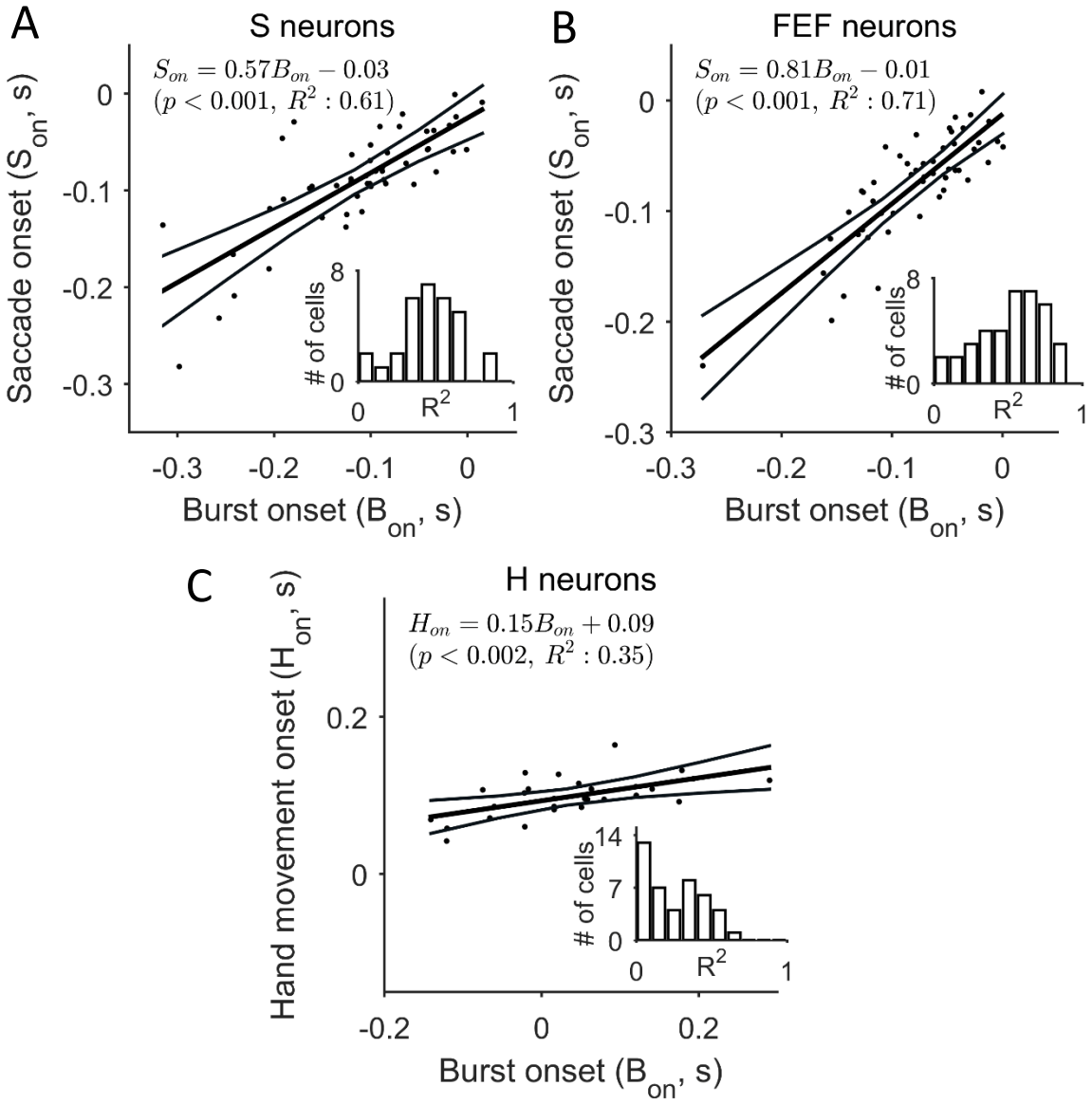


Figure 23. Examples of the relationship between discharge onset (B_{on}) and movement onset (S_{on}) for an S (R287 in A), an FEF (R264 in B) and an H (R45b in C)

Hand related neurons (H)

The discharge of 43 neurons of the periarcuate cortex preceded hand movements in the direction they preferred whether these were accompanied by saccades or not (Fig. 3C, Table II). Figure 24 provides an example of the discharge of such a neuron (R225) for hand movements of two different sizes (10 and 20 deg) in eight different directions. As shown here, this neuron preferentially discharged for upward movements of the hand. When its discharges were fitted to the von Mises distribution (see above), its on-direction was found to equal 101° in the hand task and 121° in the eye/hand task, a difference that was not statistically significant (p=0.33, Watson-Williams test). With one exception, this was true of all H neurons in our sample; their on-directions were the same whether estimated using the hand or the eye/hand tasks. The width of the movement field ($2/\sqrt{k}$ of the von Mises distribution) of cell R225 was 183° in the hand task and 214° in the eye/hand task, a difference that also proved not statistically significant.

Figure 25 plots the preferred directions of the H neurons we studied. Use of the Rayleigh test failed to disclose departure from uniformity (p=0.1). To examine if H neurons differ from S neurons in terms of the lateralization of their on-directions, we counted the number of neurons with ipsiversive and contraversive on-directions after excluding those within 30 deg of the vertical meridian. H cells were as likely to be contraversive or ipsiversive as S cells (p= 0.67; chi-square test). The width of the movement fields of the H neurons (mean±SD=169±77°) was slightly wider (t-test, $p<0.05$) than the field of S cells (mean±SD=135°±66; see S neurons above).

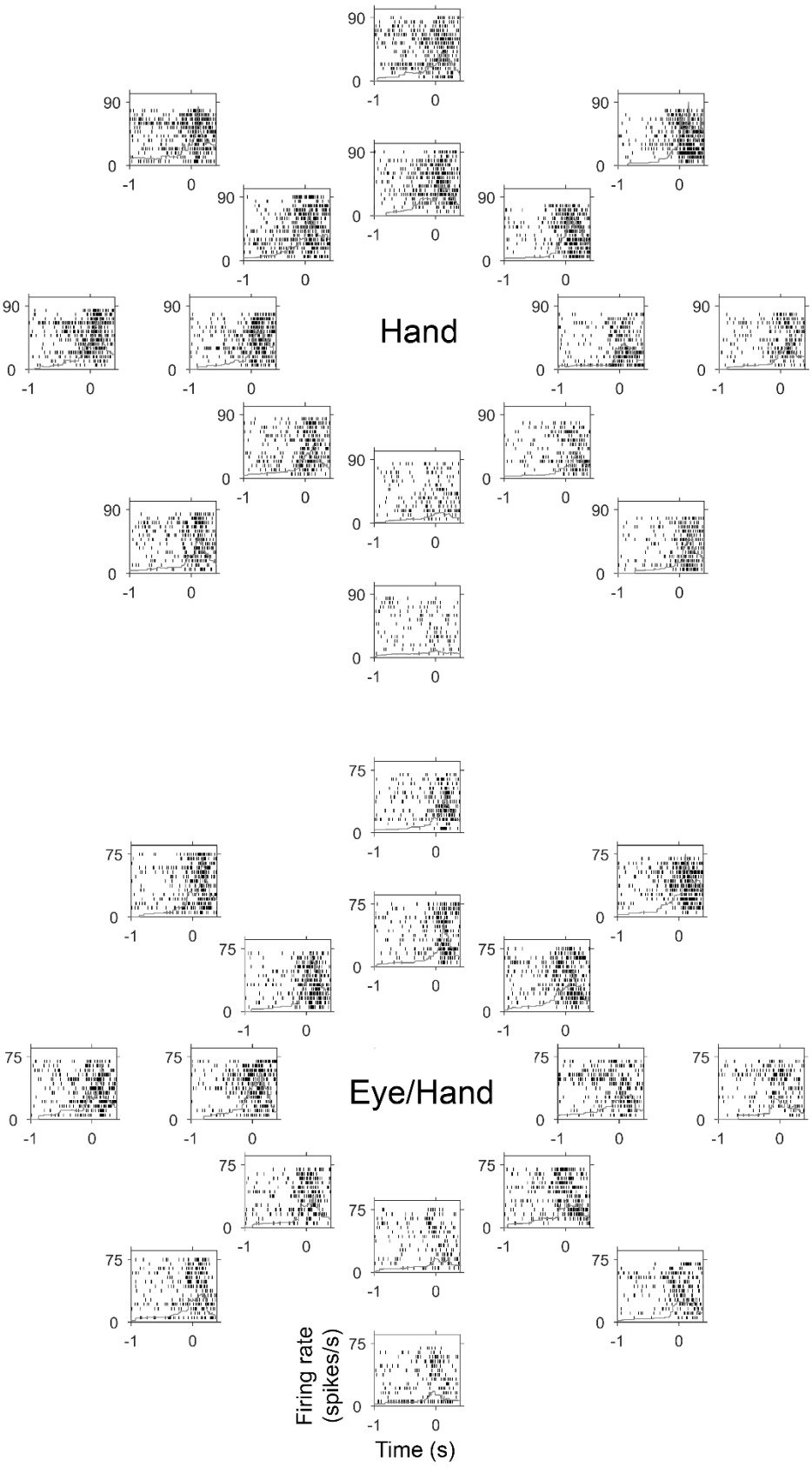


Figure 24. Example of the discharges of an H neuron (R225) during single effector (left) and joint effector (right) trials. Conventions as in Fig. 3.

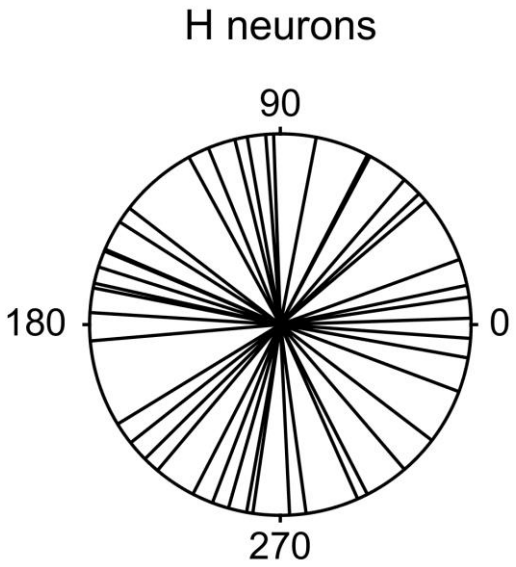


Figure 25. Distribution of the preferred directions of H neurons. Conventions as in Fig. 19A.

The latency of the discharge of H neurons ranged between 22 and 174 ms. The mean latency of the H neurons (71 ms; SD=36) was significantly shorter (t-test $p<5\cdot10^{-14}$) than that of Meq cells (mean±SD=152±51 ms) relative to the onset of hand movements in eye-hand trials, suggesting that H neurons are closer to the output of the system than Meq cells. We also wanted to examine, on a trial by trial basis, if the earlier or later onset of the discharge of H cells affected the onset of hand movements. To this end, we plotted discharge onset against hand movement onset after aligning the joint effector trials onto the onset of saccades. Figure 23C shows an example (from cell R45b) of the strong relationship between the two variables we found in many H cells. The inset plots the variance of this relationship in the 43 H neurons we examined. It was statistically significant ($p<0.05\text{-}5x10^{-8}$), ranging in value between 5 and 66%, in 29 H neurons. Their percentage (29/43) was higher than that of Meq cells (21/55) a difference that was statistically significant (chi-square=12.34, $p<0.005$). When present, the relationship between discharge onset and hand movement onset was more robust in H cells as indicated by their higher R^2 values relative to those of Meq cells ($p<0.05$, Mann-Whitney), again suggesting that H cells are closer to the output of the system. In fact, 11 of the remaining 14 H cells displayed a statistically significant correlation

between the onset of their discharge and the onset of hand movements in single effector trials aligned on the GO signal.

Other neurons (xS, xH, XOR, AND)

Besides Meq, S and H neurons the premotor cortex contains a small number of eye-hand related cells with more complex discharge patterns (Fig. 3). Five cells displayed increased activity for saccades only if they were executed in isolation; they did not discharge when saccades were accompanied by hand movements (Fig. 3D) and are for this reason labelled xS (exclusive S). Such neurons seemed to be actively inhibited during movements of the effector they do not prefer, i.e., the hand in the case of xS cells. Another 3 neurons, marked as xH (exclusive H), discharged before hand movements executed in isolation and not when combined with saccades (Fig. 3E). Two other neurons discharged only for coordinated eye-hand movements but not when the two effectors moved independently (Fig. 3F). These cells are reminiscent of the AND gate of digital electronics which produces an output that is true only if all its inputs are true, and are for this reason marked as AND cells. Finally 3 neurons, discharged for saccades or hand movements when executed independently but not for coordinated eye-hand movements (Fig. 3G). They are referred to as XOR cells because they are reminiscent of the XOR logical gate which implements an exclusive or, i.e., its output is true if one, and only one, of its inputs is true. Because of the extremely small number of such cells the following few paragraphs provide a brief description of their firing properties as a group.

Figure 26 shows a distribution of the preferred directions and provides examples of the movement fields of these rare cells, separately for eye (left) and hand (right) movements. Those belonging to exclusive cells (xS: magenta, xH: turquoise) were assigned to the plot that concerns the effector they accompanied (R32: Eye; L5: Hand). XOR cells (such as R75), on the other hand, had distinct movement fields for saccades and hand movements (green). Because they discharged only when both the eyes and the hand moved together, AND cells (such as R76) were assigned to both plots (yellow). As a group, this collection of rare cells seems to represent a wide range of directions in both hemifields.

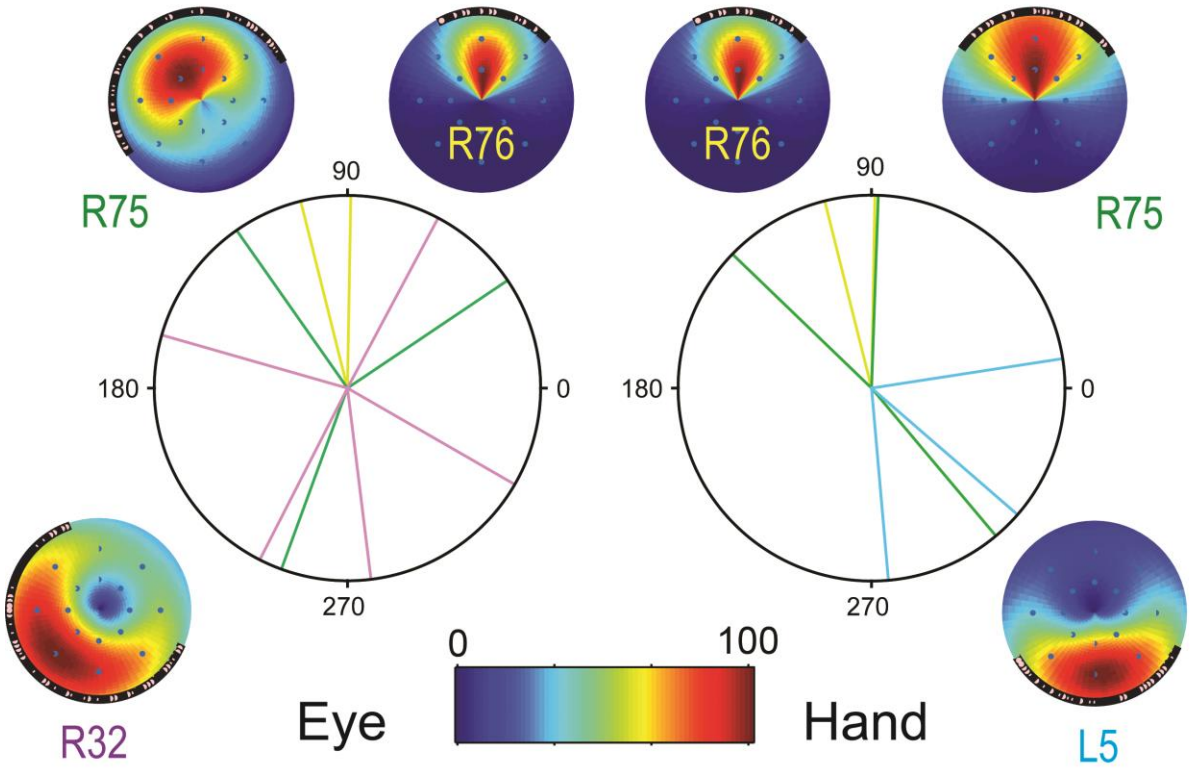


Figure 26. Distribution of the preferred directions of XOR (green, R75), AND (yellow, R76), xH (turquoise, L5) and xS (magenta, R32) neurons. We used the same color code to assign the movement fields illustrated to the neurons they belong to. Movement fields were found from 2D surface fits to their mean rate of discharges during the movement epoch in saccade trials (left) and hand movement trials (right). Surfaces were the product of Gaussian (for amplitude) and von Mises (for direction) distributions and the parameters that best fit the data were found with the least-squares method. The color scale in the center is proportional to normalized intensity of discharge.

The intensity of the discharge of the AND, XOR, xS and xH neurons ranged between 10 and 110 spikes/s. We obtained these values in saccade trials for xS neurons, hand trials for xH neurons, eye-hand trials for AND neurons and the mean intensity of the discharges they emitted in single effector (eye or hand) trials for XOR neurons. On the average (44 spikes/s, SD=29), it did not differ significantly from that of H ($p=0.76$, t-test) and S ($p=0.053$, t-test) neurons. To compare the duration of their

discharge to that of S and H neurons, we calculated two averages. The first, which we compared to that of S neurons, was found from AND neurons in eye-hand trials, and xS neurons as well as XOR neurons in saccade trials (mean±SD=213±129 ms). The second, which we compared to that of H neurons, was found from AND neurons in eye-hand trials, and xH neurons as well as XOR neurons in hand movement trials (mean±SD=257±131 ms). Neither comparison proved statistically significant (p=0.25 and 0.13, respectively; t-test). The latency of discharge of AND, XOR, xS and xH neurons (range: 8 – 126 ms) is shorter than that of Meq neurons and roughly similar to that of S and H neurons. With the exception of 2 of the xH neurons, discharge onset was well correlated to movement onset. Figure 25A illustrates an example for one of the AND cells (R76). As shown here, the onset of its discharge was well correlated with the onset of hand movements (R^2=0.62, p<0.001) when both are aligned to the onset of saccades. It was also well correlated, albeit not as strongly, with the onset of saccades (R^2=0.25, p<0.005) when both are aligned to the onset of hand movements. To explore the relationship between the onset of the discharge of XOR, xS and xH neurons and the onset of effector movement we relied on single effector trials after aligning neural and behavioral events on the Go cue. Examples of significant correlation between the onset of their discharge and the onset of saccades (R^2=34, p<0.001) or hand movements (R^2=33, p<0.001), are shown in Figs. 27B and 27C for one xS (R347) and one xH (L5) neuron, respectively. Finally, the onset of the discharge of the XOR cells was well correlated with the onset of hand movements (e.g., Fig. 27D) and not to the onset of saccades but we encountered few such neurons to be able to reach definite conclusions.

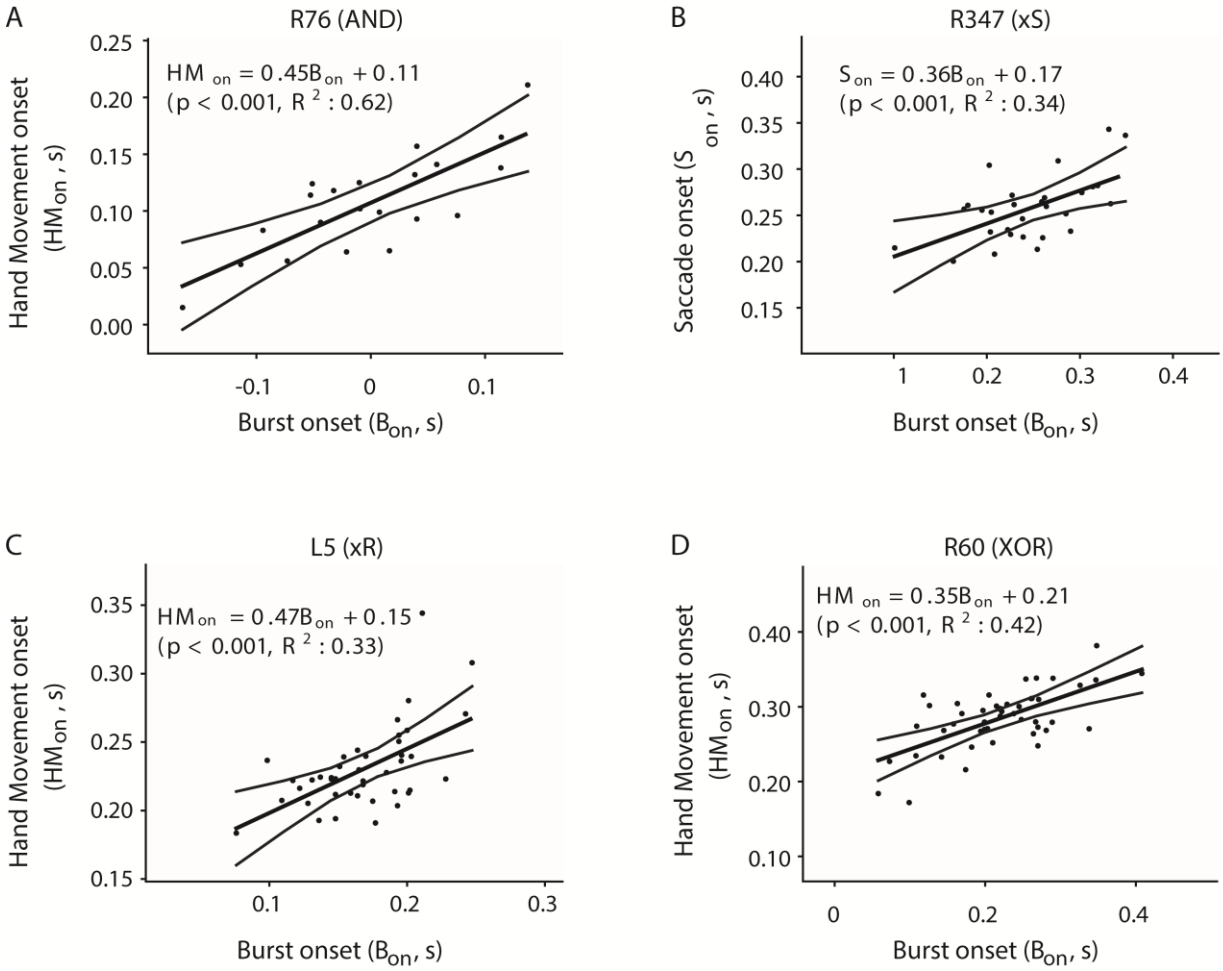
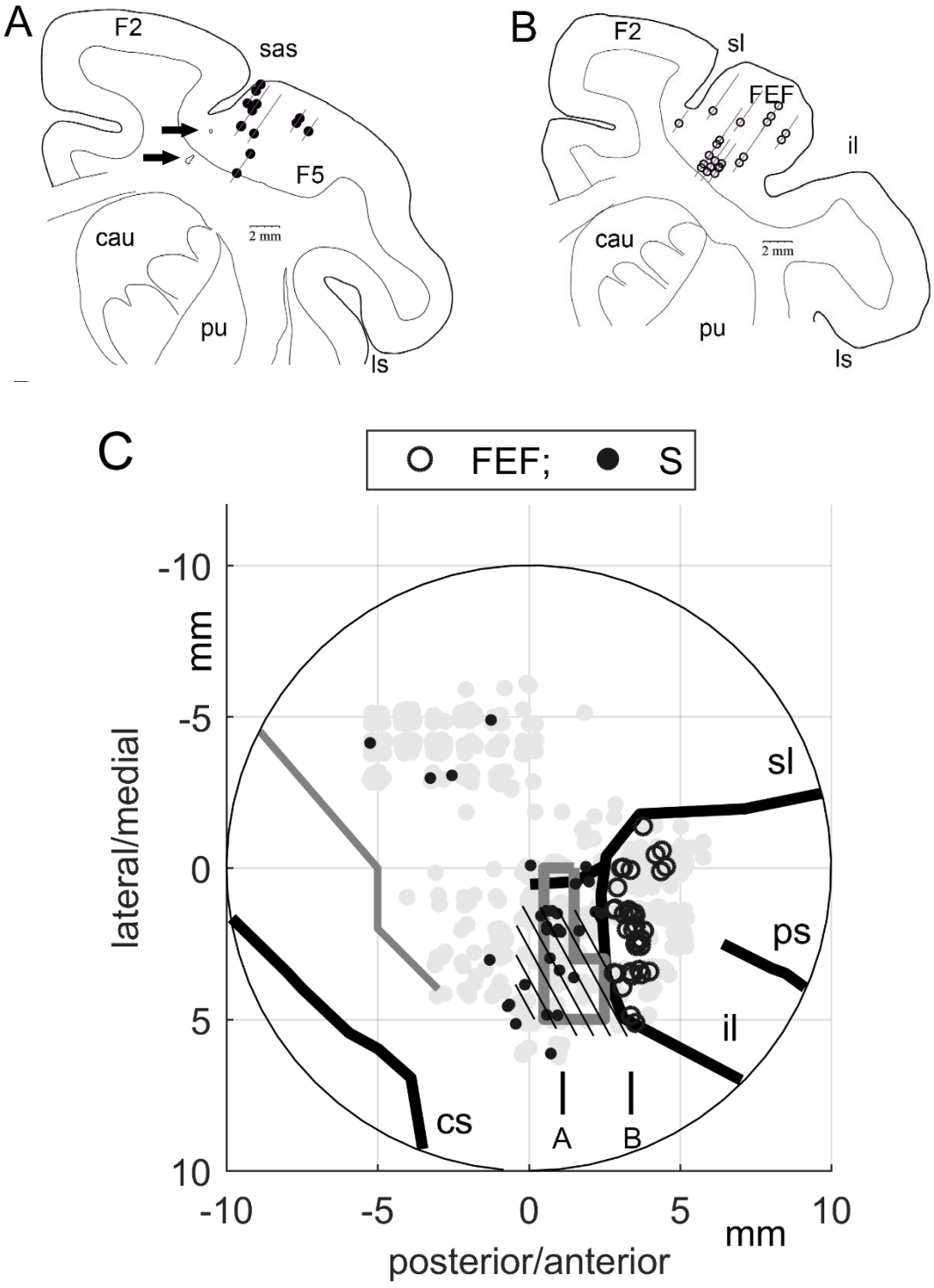


Figure 27. Scatter plots of movement onset (ordinate) versus discharge onset (abscissa) of AND (R76 in A), xS (R347 in B), xH (L5 in C) and XOR (R60 in D) neurons. Each point is from a different trial. Lines indicate the linear regression fit to the data (obeying the expression displayed) and the 95% confidence intervals.

Figure 28 illustrates the location of the S, H and FEF neurons we found in different parts of the periarcuate cortex (solid: S, open: FEF, gray: H). The location of the few xS (+), xH (x), AND (▼) and XOR (Δ) cells we encountered is also marked on the same plots. Their location relative to the AS was histologically verified in one hemisphere of monkey R. We anchored the data from all three hemispheres on the borders of area F5 (hatched) mapped for the needs of an experiment focusing on mirror neurons as well as on the borders of the smooth pursuit area (straight gray lines) mapped with the help of microstimulation. As shown here, S neurons were found in several premotor sites, but they were particularly well represented in sites belonging to the smooth pursuit area and area F5 of the caudal bank of the AS. AND,

XOR and xS neurons were found in our most caudal recording sites, near areas where skeletal movements were elicited with currents <30 μA. In contrast, H neurons were more evenly distributed through the premotor cortex.



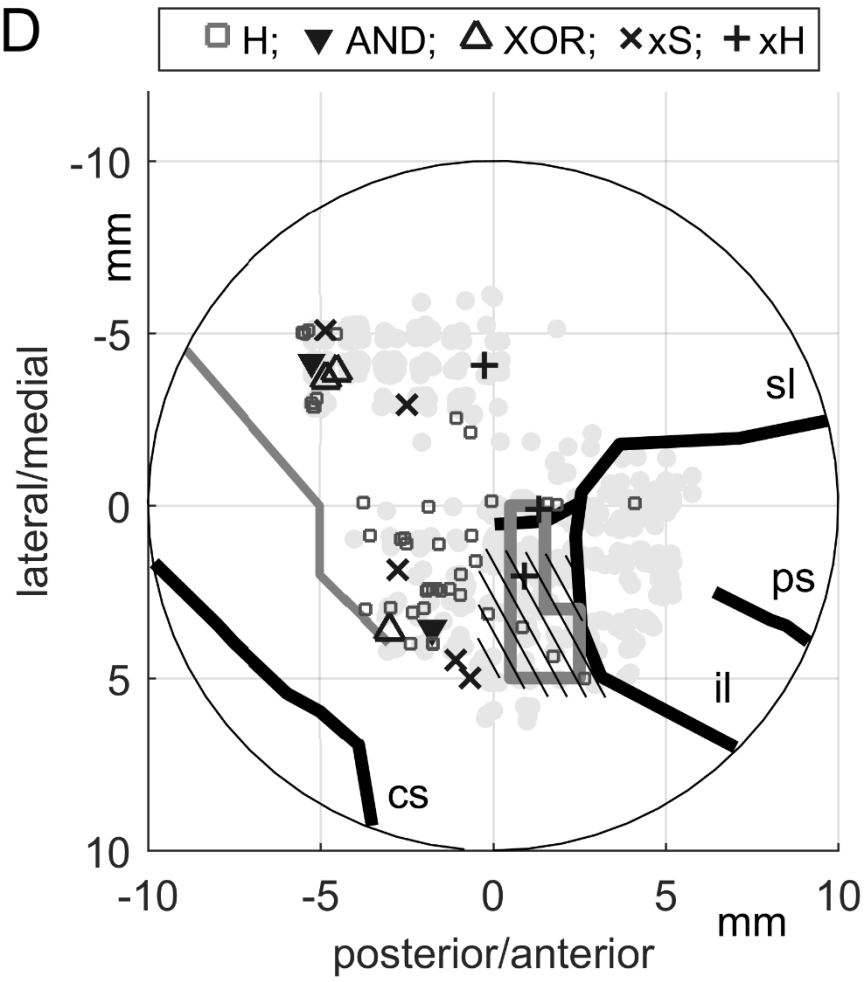


Figure 28. Location of the neurons we encountered in the primate periarcuate cortex relative to the AS and arranged on a grid centered on the middle of our recording chamber. (A, B) Frontal sections through the premotor (A) and the prearcuate (B) cortex of subject R. Their relative location is indicated in C. (C) Location of FEF (open) and S (solid) cells. (D) Location of H (open squares), XOR (Δ), AND (▼), xH (+) and xS (x) neurons. Other units encountered are shown as light gray circles. Symbols were slightly moved to avoid clutter. Data are from 3 hemispheres aligned relative to the borders of the smooth pursuit area (thick gray lines), the border between primary motor and the premotor cortex (thin gray line) and area F5 (hatched). Arrows in (A) point to electrolytic lesions placed in subject R just prior to perfusion to anchor the relative location of electrode tracks. Abbreviations: cs, central sulcus; il, inferior limb of the AS, ps, principal sulcus; sas, spur of the AS; sl, superior limb of the AS, cau: caudate, pu: putamen.

Microstimulations

A total of 232 sites from subject R and 89 sites from subject L were stimulated. Figure 29 provides examples of typical saccades evoked in response to identical electrical stimuli applied to a site (marked with an arrow in Fig. 34) in the right post-arcuate cortex of a monkey (subject R). Ninety-five per cent of the stimuli delivered at this site were followed by saccades. The examples included in Fig. 29 have been arranged from left to right in order of initial horizontal eye position. As shown here, the size of their horizontal component decreases as the eyes start from progressively more rightward initial positions and they reverse direction when the starting position exceeds a certain eccentricity, roughly equal to 20° to the right of straight ahead. Figure 30A shows an XY plot of the trajectories of saccades elicited from another site (marked with a triangle in Fig. 34) within 80 ms of the onset of the stimulation (their latencies are shown in Fig. 30B). 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 (ipiversive) 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. 31 we plotted the size of their vertical component (ΔV) as a function of initial vertical eye position (V_I). The solid line is the linear regression line through the data and obeys the expression displayed in the plot. It explains most 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 fairly steep. The intercept (S_V) is the characteristic vector of saccades evoked from this site (McIlwain, 1988). Its value (-13.7°) indicates that had the eyes started from straight ahead they would move down by almost 15 °. The horizontal components of the same saccades (ΔH) were less sensitive to the initial horizontal eye position (H_I) 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. 31B). 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.

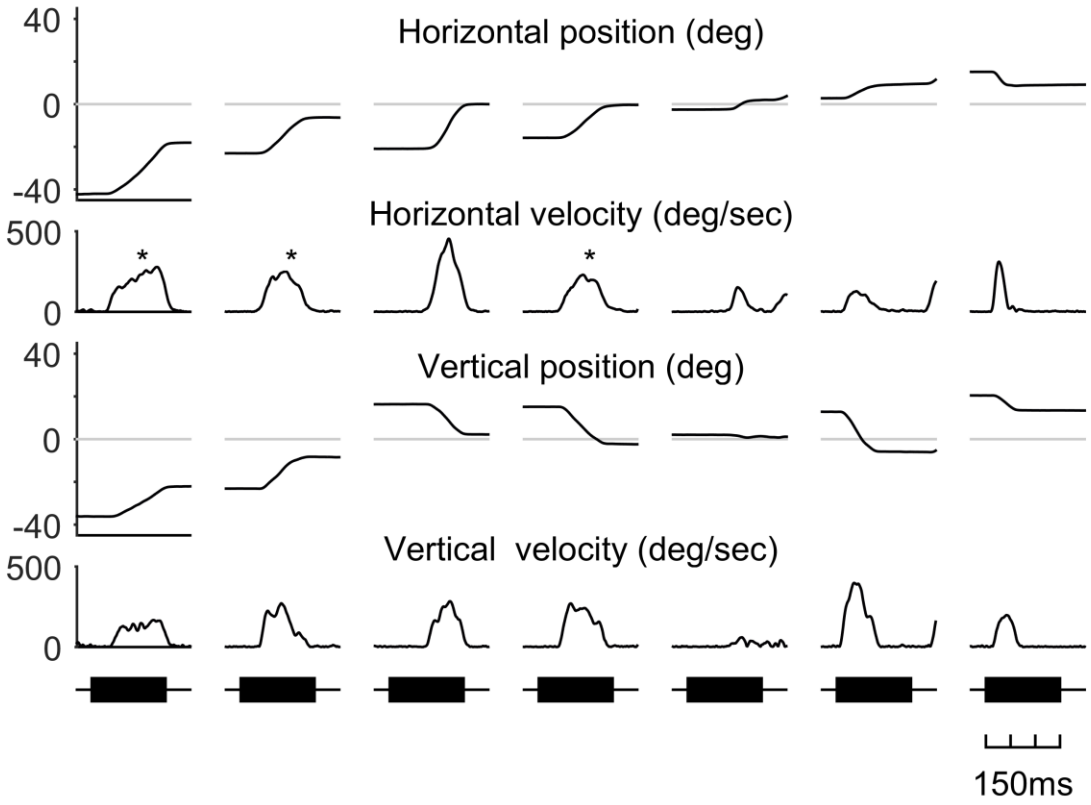


Figure 29. Examples of eye movements evoked in response to identical electrical stimuli (45 pulses of 80 μA) delivered at a single site of the right premotor cortex of subject R. Gray lines indicate zero horizontal (top) and vertical (bottom) position. Boxes underneath the vertical instantaneous velocity traces indicate the duration of the stimulus trains. Flattened velocity profiles are indicated with asterisks.

In contrast, saccades evoked from the frontal eye field (FEF) were mainly contraversive. An example is shown in Fig. 32A, which is an XY plot of the trajectories of saccades elicited from a site (marked with an asterisk in Fig. 34) of the right FEF of the same subject that generated the movements shown in Figs. 29-31. Here again, identical stimuli applied to a single site evoked a large variety of leftward (contraversive) saccade vectors that collectively converge towards a "goal area" which in the case of Fig. 32 is down and to the left of straight ahead. Because their horizontal (k_H=0.44, R^2= 0.54) and the 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 illustrated in Fig. 32B and Fig. 32C, respectively. The S_H (-12.9°) and S_V (-2.2°) values we obtained indicate that they were indeed leftward (contraversive) and downward.

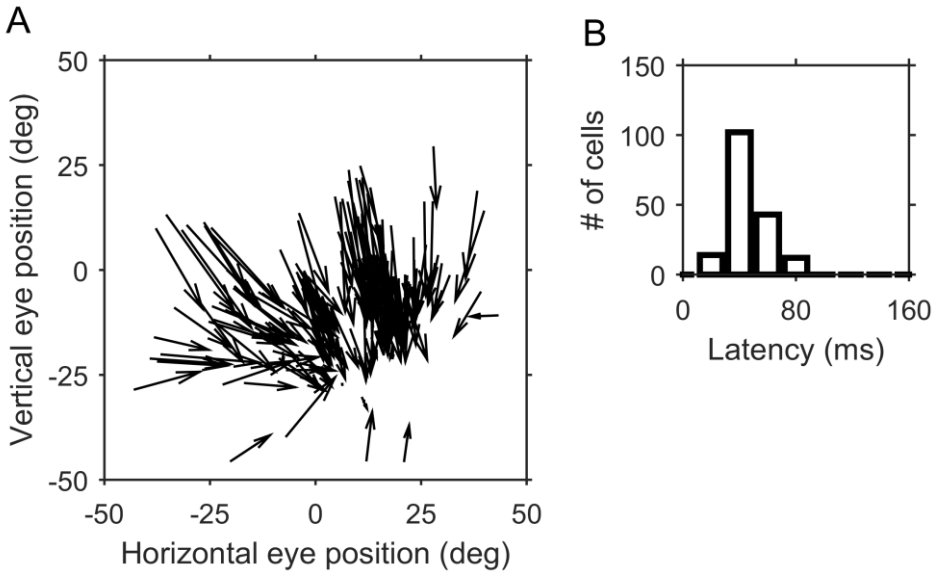


Figure 30. A) XY plot of the saccades evoked in response to the electrical stimulation of a PMv site (in subject R). Each arrow starts from the initial position of the eyes (H_1) and its arrowhead points to the position reached after the end of the saccade. B) Distribution of the latencies of evoked saccades.

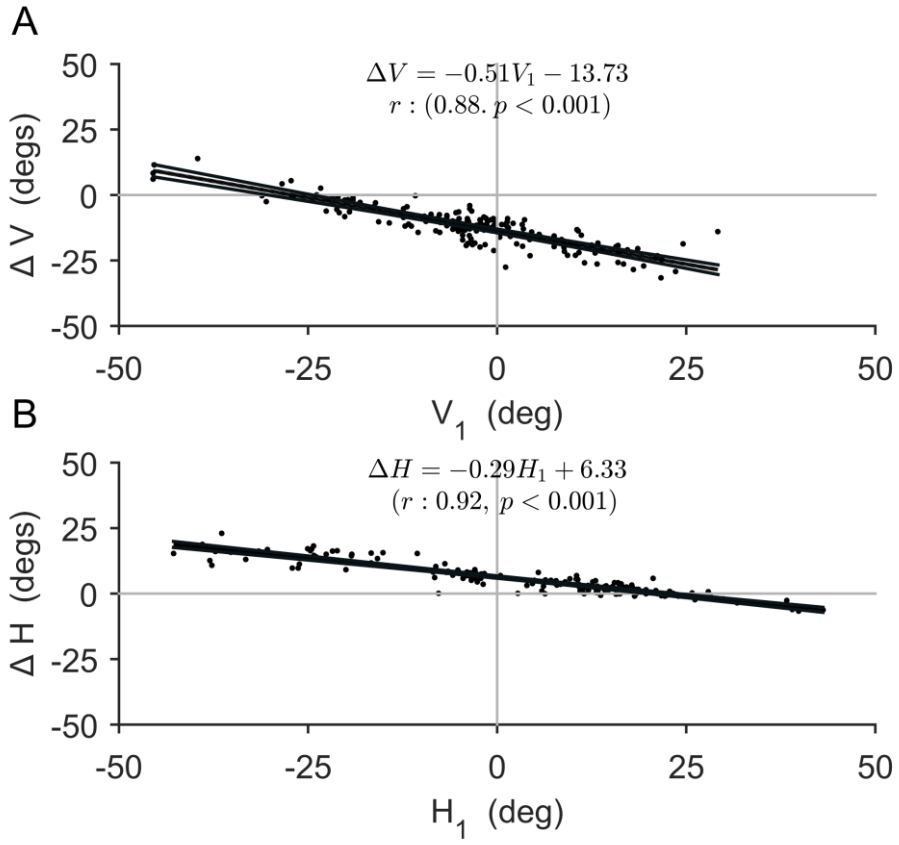


Figure 31. Plot of the initial vertical (V_1; A) and horizontal (H_1; B) position of the eyes (abscissa) versus the vertical (ΔV; A) and horizontal (ΔH; B) displacement of saccades (ordinate) evoked in response to the electrical stimulation of the same PMv site as in Figs. 30. The solid straight lines are the least-squares regression lines through the data and obey the expressions displayed. The curved lines are the 95% confidence intervals; the closer to the linear regression line the stronger our confidence in its slope and intercept.

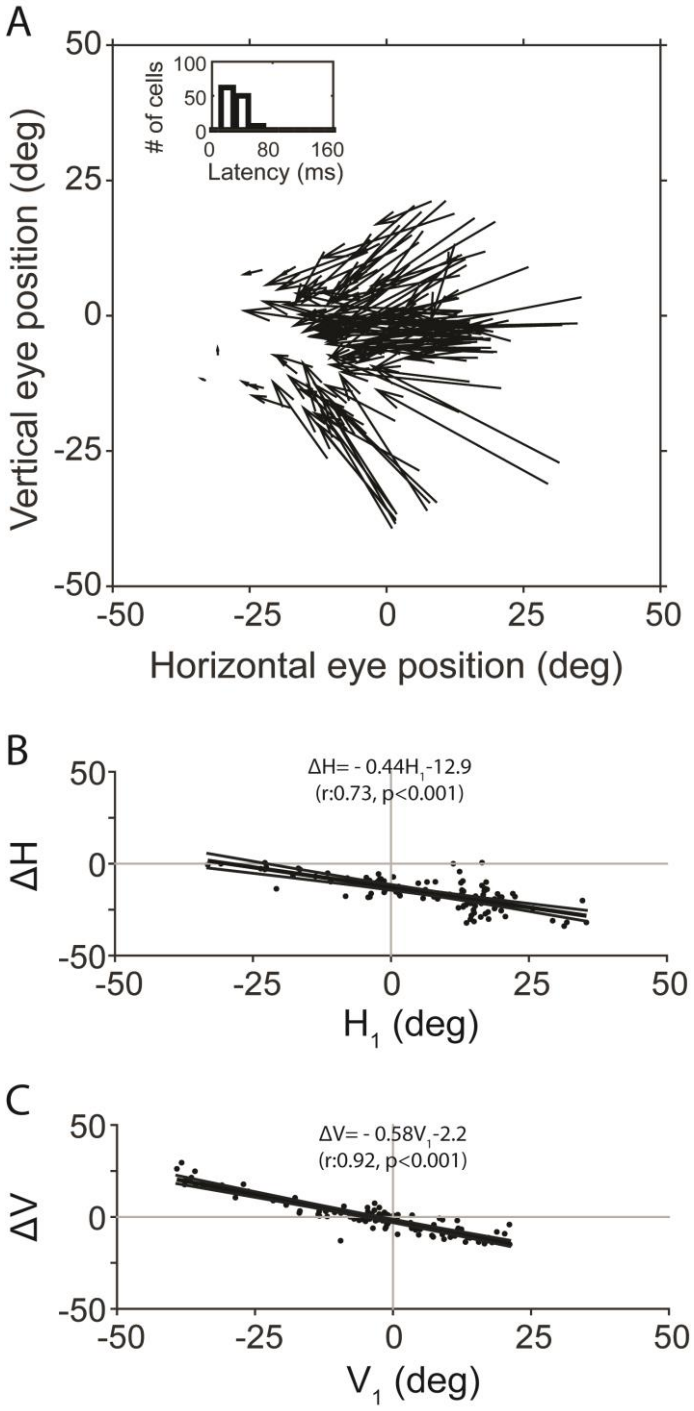


Figure 32. A) XY plot of saccades elicited by electrical stimulation of an FEF site. Conventions as in Fig. 2. The inset is the frequency histogram of the latencies of evoked saccades. B, C) Plot of initial horizontal (H_I; B) and vertical (V_I; C) position of the eyes (abscissa) versus the vertical (ΔV; B) and horizontal (ΔH; C) displacement of saccades (ordinate) evoked in response to the electrical stimulation of the same FEF site. Conventions as in Fig. 30 & 31.

As shown in Fig. 29 (asterisks), the velocity profiles of post-arcuate evoked saccades could be relatively shallow and display multiple peaks. Figure 33 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: 109 s^{-1} & 105 s^{-1}) provided excellent fit to 153 ipsiversive (blue) and 1362 contraversive (red) saccades, respectively, electrically evoked from 19 FEF sites (R^2: 0.88 and 0.86, respectively). Saccades evoked from 32 post-arcuate sites were slower. Here, significantly smaller α values ($p<10^{-8}$; post-hoc ANCOVA) equal to 82 s^{-1} and 75 s^{-1}, respectively, had to be used, while keeping β equal to 0.62, to fit the 1983 contraversive (red) and 998 ipsiversive (blue) saccades evoked from them (R^2: 0.82 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 in response to the electrical stimulation of its premotor cortex.

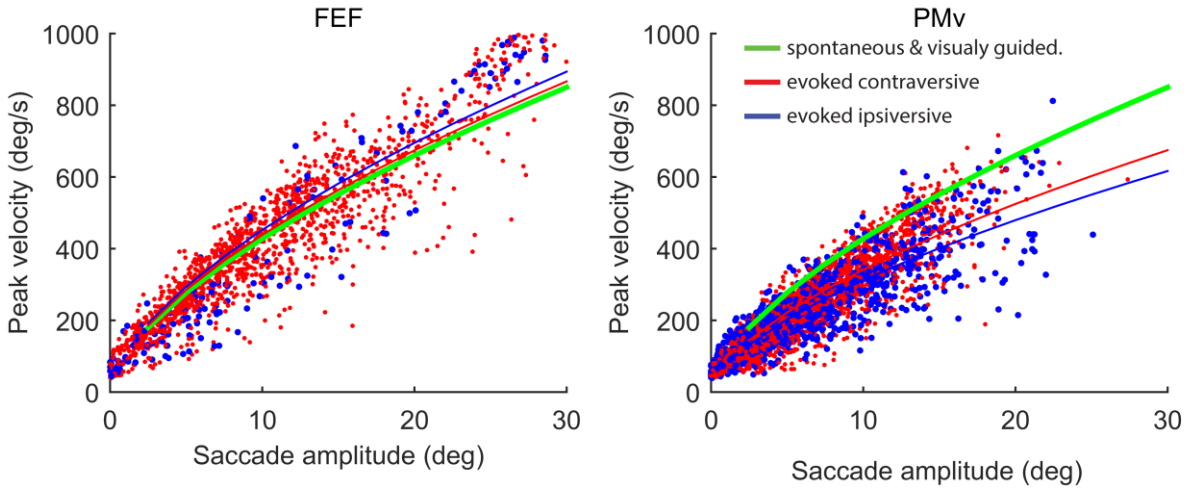


Figure 33. Plot of peak radial velocity (ordinate) versus saccade amplitude (abscissa) for contraversive (red) and ipsiversive (blue) saccades evoked in response to electrical stimulation of anterior (A) and posterior (B) sites of the right frontal lobe of a monkey. The green, red and blue lines are the power law fits to spontaneous/visually guided, contraversive electrically evoked and ipsiversive electrically evoked, respectively, saccades executed by this subject.

Figure 34 is 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. Thirty seven of these penetrations evoked saccades with thresholds as low as 20 μA. They contained 20 sites that were found in the FEF and 32 in the caudal bank of the AS and the arcuate spur following histological verification of their location (see below). Five more sites were found near the surface of the AS. Because their electrical stimulation could activate parts of both of its banks, saccades evoked from them were excluded from further analysis. Finally, in agreement with previous observations (Fujii et al., 2000), we found two saccade evoking sites in the rostral and dorsal premotor cortex 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 in order to study their properties.

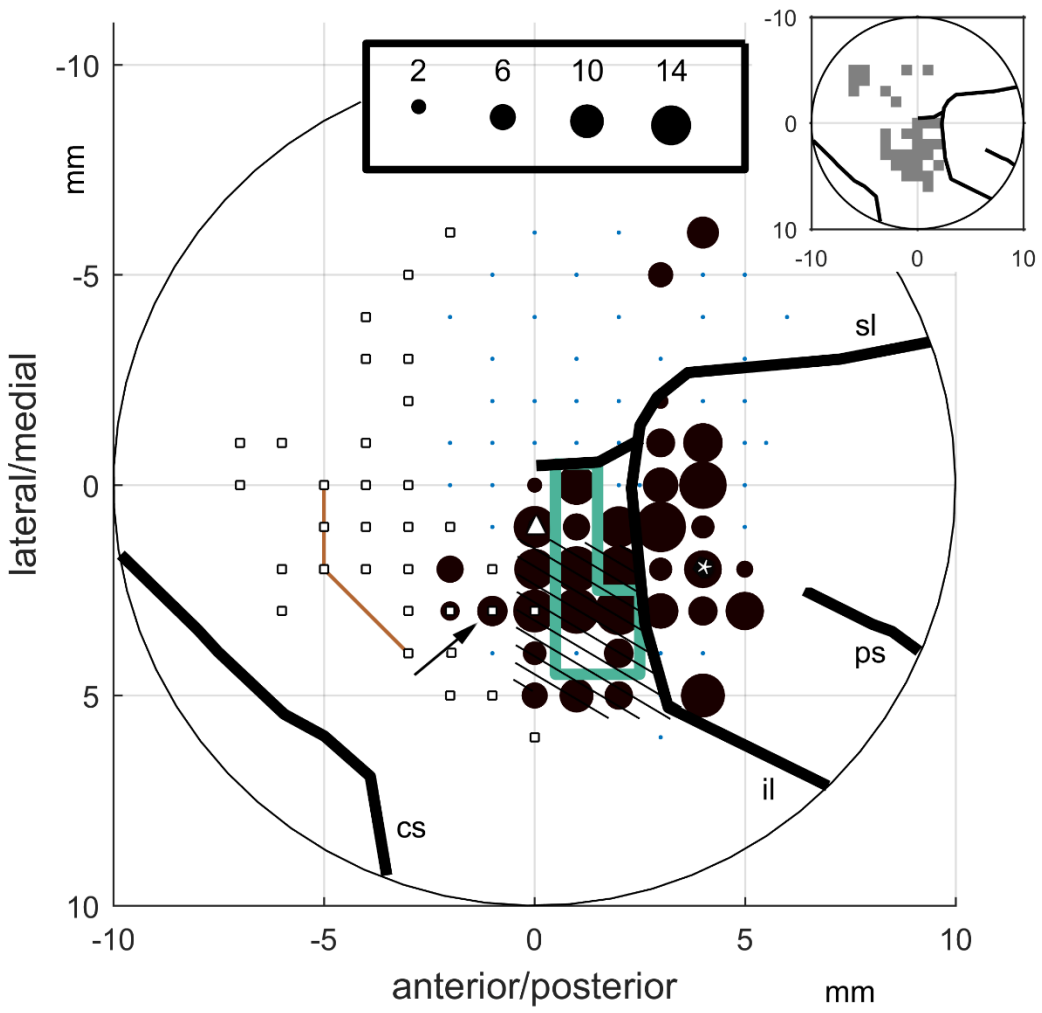


Figure 34. Map of penetrations through the right hemisphere of one monkey. They are marked depending on whether they evoked saccades (solid circles), skeletomotor movements (open squares) or were not effective (dots). The radius of the solid circles is proportional to the likelihood that electrical stimulation of a site would evoke saccades (in terms of a standard score σ_i, see text for a description). Orange lines indicate the rostral border of M1. Green lines indicate the smooth pursuit area. An arrow points to the track that generated the saccades illustrated in Fig. 29. Other symbols mark the tracks that generated the data for Figs. 30, 31 (triangle) and 32 (star). Abbreviations: cs, central sulcus; il, inferior limb of the arcuate sulcus, ps, principal sulcus; sl, superior limb of the arcuate sulcus. The inset illustrates the sites of the postarcuate cortex, where neurons discharging before saccades were isolated.

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 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 (i) was assigned a standard score (in multiples of SD), σ_i, indicative of the likelihood that its electrical stimulation evokes saccades. A value of σ_i, equal to 2 corresponds to a probability that the null hypothesis (i.e., that the movements generated during a stimulation session are coincidental spontaneous movements and not evoked) is true <0.05 while a value equal to 5 corresponds to a probability $<6\times10^{-7}$. Sites that evoke saccades easily in response to electrical stimulation display large values of σ_i while sites that seldom evoke saccades display small values of σ_i. In Fig. 34, these values 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).

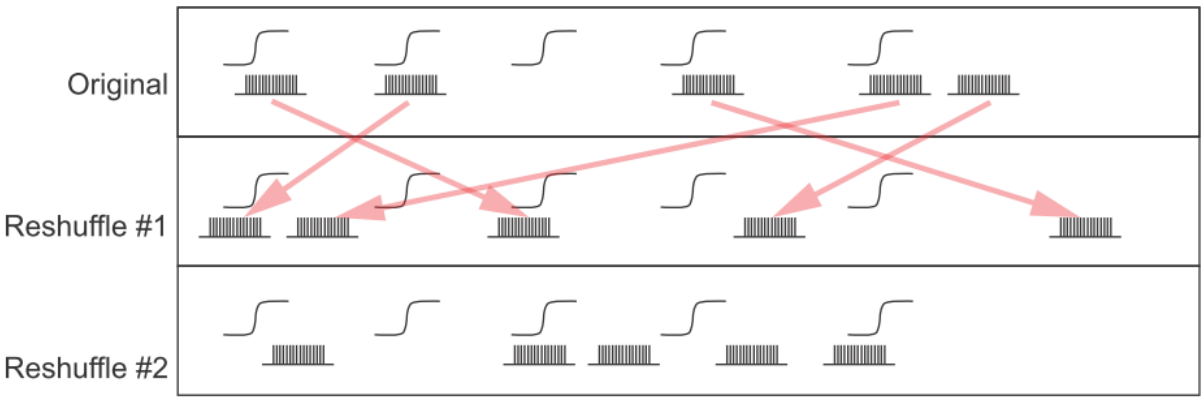


Figure 35. Illustration of the reshuffling process that was employed by the Monte Carlo estimate of the incidence rate by spontaneous saccades. Step-up curves represent eye traces of evoked movements, while the comb-like impulse trains represent the microstimulation events. In each reshuffle instance, stimulation trains were assigned at random temporal locations within the behavioral record of eye movements.

Most of the sites that evoked saccades occupied an area that was contiguous and covered the rostral and lateral quarter of our recording chamber. Some of the sites that evoked saccades with high certainty (σ_i=14) were next to sites with much smaller values of σ_i (as small as 2). Caudally and medially to this region we were generally unable to evoke saccades (dots). Instead, as the electrode moved caudally it became progressively easier to evoke skeletomotor movements, usually of the upper limb and face/jaw (open squares). Note that three sites near the spur of the arcuate sulcus could evoke both saccades and skeletomotor movements (open squares embedded in solid circles). Further behind 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 (thin gray line). 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 by thick gray lines); their depth ranged from about 4 to 9 mm below the cortical surface. On occasion, the slow eye movements evoked from them were interrupted by small saccades and, following saccade offset, they continued till the end of the stimulation.

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. 36A. 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) for the duration of the stimulation. Saccades evoked from nearby sites were also ipsiversive. An example is shown in Fig. 36B-D, which displays data obtained in response to the electrical stimulation of the same site. Figure 34B is 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. 36B 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 similarly obtained from the linear regression lines illustrated in Fig. 36C and Fig. 36D, 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.

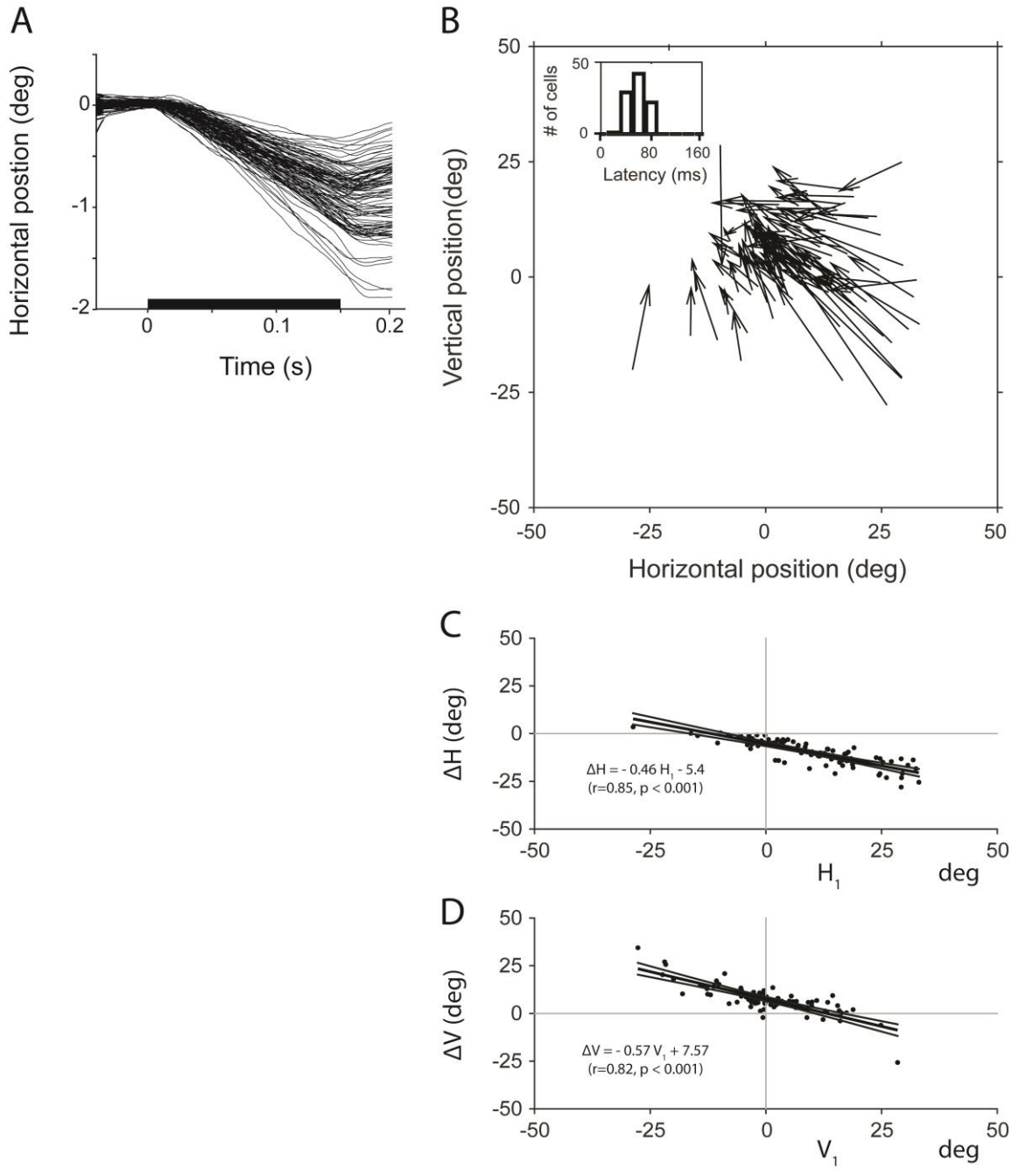


Figure 36. A) Superposition of the horizontal component of slow eye movements generated in response to the same electrical stimulation (again 45 pulses of 80 μA) of a site in the left hemisphere of subject L. All records were vertically aligned around the straight ahead horizontal position. Black bar indicates the duration of the stimulation. B) XY plot of saccades

elicited by electrical stimulation of another site of the same hemisphere of subject L. Conventions as in Fig. 29. Their latencies are shown in the inset. C, D) Plot of initial horizontal (H_1; C) and vertical (V_1; D) position of the eyes (abscissa) versus the vertical (ΔV; C) and horizontal (ΔH; D) displacement of saccades (ordinate) evoked in response to the electrical stimulation of the same site. Conventions as in Figs. 30 & 31.

To summarize, comparison of Fig. 36 to Figs. 30 and 31 indicates that the characteristic vector of saccades evoked in response to stimulation of FEF sites were contraversive while those of post-arcuate sites were ipsiversive. Figure 35 uses a color code to plot the direction of the characteristic vector of saccades evoked from the sites shown in Fig. 34. Characteristic vectors of evoked saccades were drawn to scale (proportional to their size) and are shown as starting from the chamber coordinates of the penetration responsible for evoking them. Sites of the same penetration that differed in depth (by at least 1 mm) are shown as giving rise to more than one vector. In addition, Fig. 35 retains the symbols and landmarks of Fig. 34, i.e, the borders of the smooth pursuit area (thick gray), the rostral borders of M1 (thin gray), the location of sites giving rise to musculoskeletal movements (open squares) and the location of sites that proved ineffective (blue dots). Sites evoking saccades with non-negligible and contraversive $|S_H|$ ($>2.5^o$) are marked with a red square and occupy the relatively rostral part of our plot. In turn, penetrations that could evoke saccades with non-negligible and ipsiversive $|S_H|$ (again $>2.5^o$) are marked with a blue square and occupy the relatively caudal and 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 miniscule horizontal components ($|S_H|<2.5^o$). 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 arcuate sulcus between areas PMv and 8A (Savaki et al., 2015).

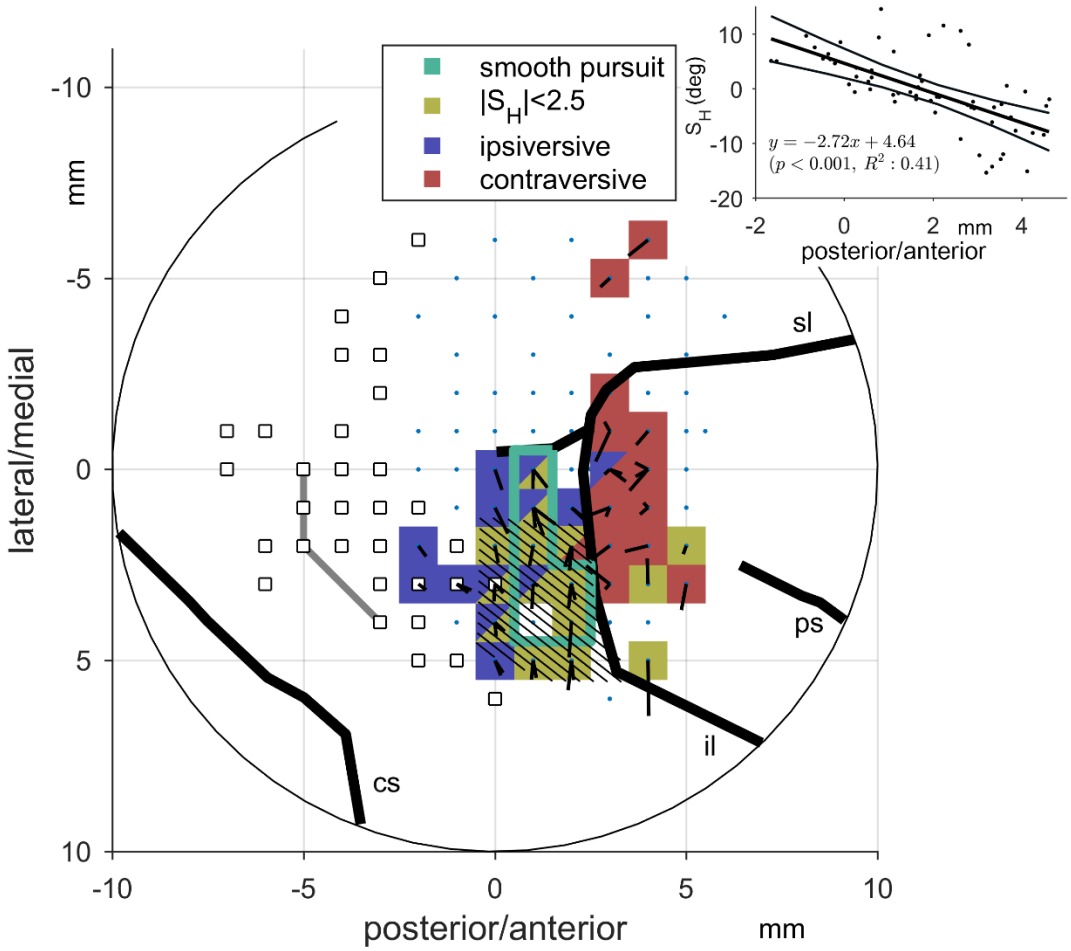


Figure 36. Map of the characteristic vectors of saccades evoked after stimulation of the same hemisphere as in Fig. 34. They are marked depending on whether their direction is contraversive (red), ipsiversive (blue) or whether S_H<2.5º (yellow). Black lines originating from each stimulation site correspond to the characteristic vector evoked from it. Multiple lines arising from the same site correspond to saccades evoked from different depths (separated by more than 1 mm). Other conventions and abbreviations as in Fig. 34. The inset depicts the characteristic vector (ordinate) in relation to the anteroposterior location (abscissa) of each recording site.

It has been argued that saccades evoked from the FEF are also more sensitive to initial eye position (Fujii et al., 1998) than those evoked from the premotor cortex 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. 38 shows the distribution of the k_H versus k_V values for saccades generated in response to stimulation of 15 FEF and 32 post-arcuate sites. It does not include data from the 2 PMd sites, and 5 FEF sites whose

displacement-position curves were too noisy to be certain of the position sensitivity of saccades evoked from them. In agreement with Fig. 3A of Fujii et al. (1998), the horizontal and vertical position sensitivities were correlated obeying the expression $k_V = 1.05k_H - 0.11$ (R^2=0.55, p<0.01). Similar expressions were obeyed when the data from the 15 FEF sites and the 32 post-arcuate sites were considered in isolation (slopes: 0.81 for the FEF and 1.18 for the post-arcuate cortex, respectively). Also 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 ($k_H = 0.01S_H - 0.28$; R^2=0.17, p<0.005). The average position sensitivity of the horizontal components of evoked saccades was -0.25 (SD: 0.14) for the FEF and -0.31 (SD: 0.1) for the post-arcuate cortex, while the average position sensitivity of the vertical components of evoked saccades was -0.34 (SD: 0.18) for the FEF and -0.45 (SD: 0.14) 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=0.09, MANOVA).

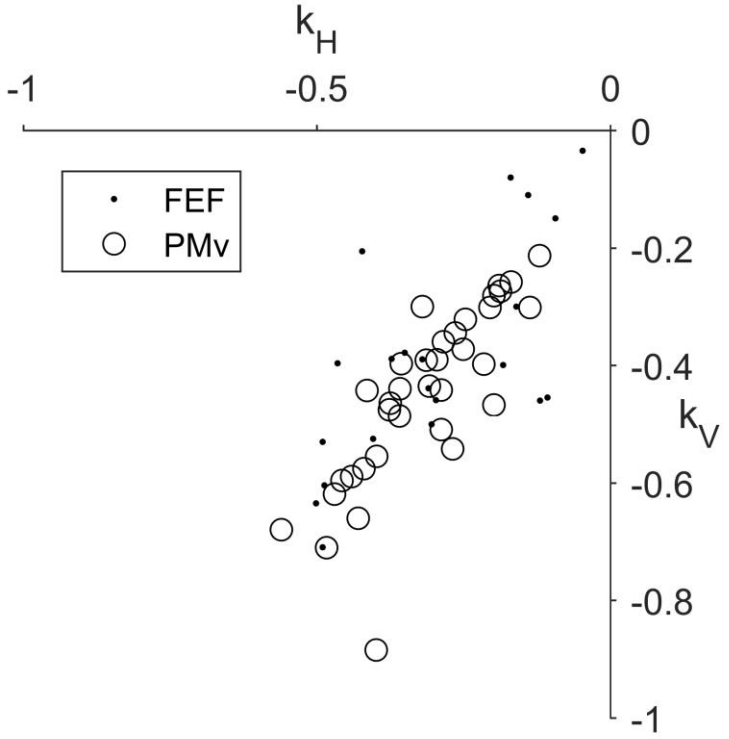


Figure 38. Plot of the horizontal position sensitivity (k_H; abscissa) against the vertical position sensitivity (k_V; ordinate) of evoked saccades. Dots indicate saccades evoked from FEF sites. Open circles indicate saccades evoked from post-arcuate sites.

Cortical stimulation sites were verified histologically in one of the hemispheres of one of the animals (subject R, which provided the data for Figs. 34 and 37). Figure 39A 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 the row at 2 mm, while the top half (above the breaks) belongs to the row at 1 mm in front of the center of the chamber in Figs. 34, 37. One of the tracks passes through two electrolytic lesions (asterisks) shown in the photomicrograph of Fig. 39B. 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 M1, and the borders of F5.

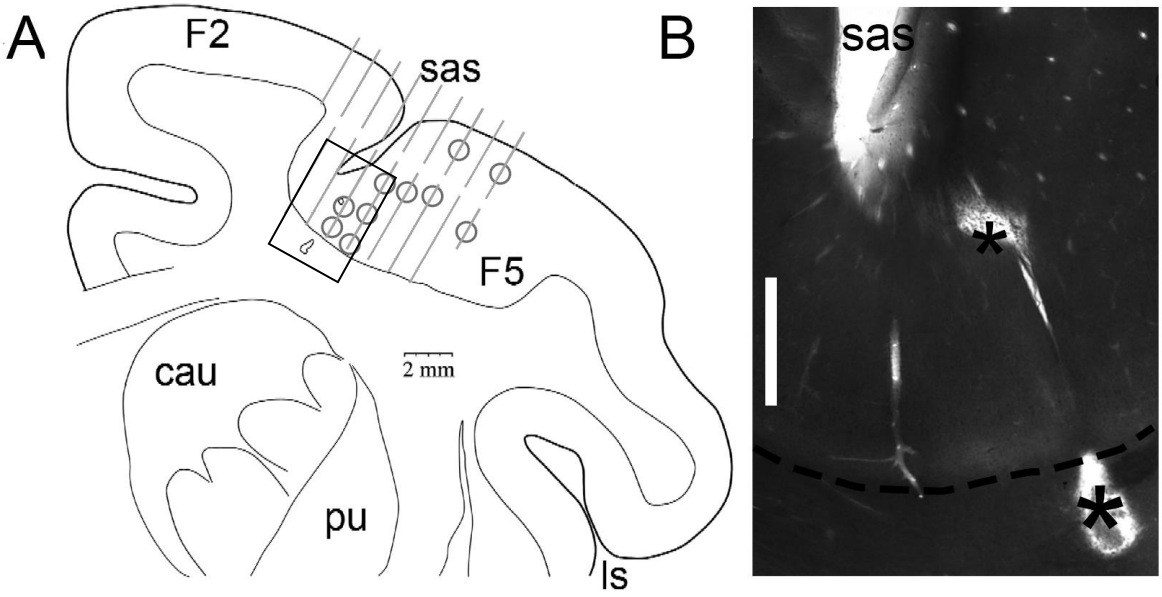


Figure 39. A. Camera lucida drawing of a coronal section passing through the lesion illustrated in B, together with the electrode tracks located within 0.5 mm of it. Electrode track segments below the break belong to penetrations 2mm anterior to the center of the recording chamber, while segments above 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. Abbreviations: Cau: caudate, pu: putamen, sas: spur of arcuate sulcus, ls: lateral sulcus.

DISCUSSION

We described the response properties of cells located in the premotor cortex and discharging phasically for saccades, hand movements and coordinated movements of the eyes and hand. The relatively high rate of their discharges started before the onset of movement of both effectors and could therefore drive either. We refer to these cells using Lashley's term (1930) motor equivalence to emphasize the notion that they could encode an abstract, effector invariant form of the vector of desired effector displacement. In contrast to Lashley, who used the concept "equivalence of motor responses" as an argument against what he called "the doctrine of the specialization of nervous elements", we are of the opinion that even the execution of equivalent motor acts can rely on specialized neural substrates. We were not surprised to see that the discharge of about a third of all task related neurons in our sample preceded hand movements in the direction they preferred whether these were accompanied by saccades or not (H neurons). The discharge of H cells was not lateralized, in that cells with ipsiversive on-directions were roughly as numerous as cells with contraversive directions. Discharge onset was correlated to the onset of hand movements for the majority of such neurons (29/43). On average the latency of their discharge relative to the onset of hand movements in eye-hand trials (71 ms) was significantly shorter (t-test $p<5\cdot10^{-14}$) than that of Meq cells (152 ms). The present study demonstrates that the premotor cortex also contains several neurons discharging before and during saccades (S neurons), whether these are accompanied by hand movements or not. In contrast to FEF cells, but similar to Meq and H cells, S cells exhibited on-directions with no preference for contraversive movements. S neurons discharged less briskly, but for longer durations than FEF cells. The onset of their discharge preceded that of FEF neurons and was about as well correlated with the onset of saccades as that of FEF neurons. A small population of neurons seemed to encode logical operations on effector combinations and might have a role in effector selection. All in all, our data demonstrate that the premotor cortex, and in particular PMv, participates in the generation of saccades.

Motor equivalence neurons

Comparison to previous studies

This is not the first report to describe cells of the premotor cortex whose phasic discharges accompany movements of the eyes as well as movements of the hand. Mann and his colleagues (1988) found such cells in the SEF and used the term "motor equivalent" to refer to their responses. Fujii et al. (2002) also encountered them in the SEF, as well as in the pre-SMA and the SMA and they provided illustrations of typical examples in Fig. 4C (a pre-SMA neuron) and Fig. 5C (SEF neuron). Although fewer, they were found in the dorsal premotor cortex (PMd) as well (Fujii et al., 2000); eighteen (9%) of the cells in the rostral PMd (corresponding to area F7 of Matelli et al.; 1998) excluding the SEF, and another 9 (3%) in caudal PMd (corresponding to area F2; Matelli et al 1998). Although focusing on tonic, delay period discharges of neurons located in the dorsal premotor cortex, rather than on phasic, movement related ones, Pesaran et al. (2010) illustrated cells that emitted bursts of roughly equal strength for reaches and saccades. Nor are effector independent discharges of premotor cortex neurons limited to eye-hand coordination; the PMd contains cells discharging for movement direction whether the effector is the ipsilateral or the contralateral arm (Cisek et al., 2003) while the PMv contains cells discharging for grasp whether executed by the ipsilateral or the contralateral hand (Rizzolatti et al., 1988). However, this report is the first to provide a detailed description of the movement field, duration, intensity and latency of the phasic discharges of Meq neurons.

The responses of Meq neurons are not lateralized in the sense that their preferred directions were as likely to be ipsiversive as contraversive for both saccades and hand movements. Since these cells discharge phasically for both saccades and hand movements it is reasonable to ask if their movement field for saccades is similar to their hand movement related one. This question was asked before, regarding cells of area PEc, which are tuned to particular directions of reaching and saccades (Battaglia-Mayer et al., 2001). These authors did not emphasize phasic responses so it is not clear that the parietal cells they encountered display the movement related bursts characteristic of the Meq cells of the present study. Instead, they determined the preferred directions of parietal cells during several different epochs and coined the term *global tuning field* (*GTF*) to indicate that they all cluster within a limited sector of space, the GTF (Battaglia-Mayer et al., 2006). As with our Meq neurons, the GTF of

PEc cells are isotropically distributed in space. A small number of Meq like cells may have been found in the parietal reach region (PRR). Of 206 PRR cells studied, 29% (N=59) had saccade related activity but it seldom preceded saccades (14/206=7%). The preferred directions of reach related discharges were aligned to those of saccade related ones (Snyder, 2000).

The on-direction of the hand related discharges of about half of the Meq cells did not differ significantly from the one for saccades. The same is true of the bimanual cells of the PMd; the preferred direction of about half (16/29=55%) of them changed little when the task was performed with the other hand (Cisek et al., 2003). It is also consistent with the observations of Pesaran and colleagues (2010) who studied the delay period activity of PMd neurons. The rather small (19 degrees) mean difference they found between the on-directions in trials involving saccades and trials involving hand movements led them to conclude that their preferred directions tend to align. However, only half of the Meq neurons we encountered do this. The on-direction of the hand related discharge of the remaining Meq neurons differed considerably from that for saccades. Such cells may in fact have been seen before as well. For example, Fig. 3A of Pesaran and colleagues (2010) illustrates a neuron whose phasic discharges accompanied up-left reaches as well as down-right saccades. Cells of the premotor cortex are known to lack preferred direction constancy across target distances and speeds (Churchland et al., 2006). Moreover, the reach epoch discharges of about half of area 7a and dorsal prelunate cells were shown to change with eye position (Heider et al., 2010); for example, Fig. 12D of these authors illustrates a dorsal prelunate neuron that discharges for up left reaches when the subject looks straight ahead and down left reaches when the target is foveated. Finally, in agreement with previous observations, the on-direction of a small number of Meq cells was found to vary with time. Neurons of the premotor cortex have been shown to display a certain preferred direction during the instruction or reaction epoch and a considerably different one during the movement epoch (Suminski et al., 2015). We demonstrate that such shifts of preferred direction can happen within the movement epoch of Meq neurons; their preferred direction can face one way early in the movement and in a different one late in the movement. Such shifts of the perimovement discharges of have been shown for some M1 neurons (Churchland and Shenoy, 2007). In their Fig. 12 these authors illustrated a neuron whose preferred direction was almost directly rightward just before movement onset (Fig. 12*A*), it turned almost directly leftward 100 ms later (Fig. 12*B*), and became rightward again when another 100 ms had elapsed (Fig. 12*C*).

The duration and the intensity of the burst of Meq neurons for one of the effectors did not always match that for the other. Concordance or dissonance was not a trait of distinct subpopulations of Meq neurons; cells that were effector invariant in some properties (e.g., intensity) might discriminate between effectors when another parameter (e.g., duration) was considered. As expected of cells that could influence the time course of movements, the maximal firing rate of Meq neurons could be significantly correlated to peak velocity, albeit for a rather small number of cells; that of the eyes in 5 cells, of the hand in 7 cells and of both eye and hand in 2 cells. More generally, since Meq cells burst for both saccades and hand movements one might expect the intensity (R_{EH}) of the burst of spikes for coordinated eye/hand movements to equal the sum of the intensities of their bursts for single effector movements (R_E for saccades and R_H for hand movements). This was indeed the case for some of the cells in our sample but again their number was small (8/55). Instead, their bursts were about 50% weaker following a trend summarized in the expression $R_{EH} = 11.3 + 0.57R_H + 0.45R_E$ ($r=0.81$, $p< 0.001$). Hagan et al. (2012) posed a similar question regarding the delay period discharges of LIP neurons, namely whether the activity of individual neurons increased or decreased when a reach accompanied a saccade. To address this issue they studied 55 LIP neurons displaying spatially selective responses in two rhesus macaques performing memory-guided saccade or saccade-reach tasks. As with our Meq neurons, their data indicate that the higher a cell fires for saccades during the movement epoch the higher it will fire for coordinated eye-hand movements as well (Fig. 3E of (Hagan et al., 2012). Hagan et al. also found that nearly half of the cells [26/55 (47%)] showed a significant difference between the two tasks, 12 of the 26 (46%) emitting higher discharges for saccades unaccompanied by reaches and 14 of 26 (54%) neurons emitting higher discharges for coordinated eye-hand movements. In contrast, only 12 of our Meq cells showed a statistically significant difference in activity between the eye and eye-hand tasks; 9 of them increased and only 3 decreased their discharge for coordinated eye-hand movements. When the eye-hand related discharge of the Meq cells is compared to their hand related one, again the higher a cell fires for hand movements the higher it fires for coordinated eye-hand movements ($R^2=0.53$, $p<5x10^{-10}$). Again, only 13 Meq cells showed a statistically significant difference in activity between the hand and eye-hand tasks; 10 cells increased and 3 decreased their discharge for coordinated eye-hand movements.

Chang et al (2016) studied the intensity of the discharge of FEF, PRR, area 5 and LIP neurons to determine how information regarding the direction of desired movements is combined with information about the effector that would carry out the

movement. They used trials in which a cue specifying the effector (eye or hand) was shown first and then after a variable delay a second cue appeared to specify the target of the movement. They discovered that PRR cells (but not area 5, LIP and FEF cells) discharge more intensely when the hand is the intended effector. Hoshi and Tanji (2002) also described such non-linear summation patterns in PMd. Several neurons had minimal effector or direction related activity when the first cue was presented, and surpassed the background discharge only after both cues had been presented. Our study extends these observations into a particular subclass of neurons of the premotor cortex. As shown in column 4 of Table II, Meq cells of the premotor cortex can discriminate between desired effectors only in part. Again as expected of cells that could represent movement plans in an abstract, effector independent manner the phasic, movement related discharges of about 70% of these neurons do not discriminate between effectors. Actually, their discharge for coordinated eye-hand movements differs little from that accompanying isolated movements of the eyes and the hand to the same target. The discharge of the remaining 30% depended on the effector executing the movement; in eye-hand trials about half of them discharged as if they accompanied isolated movements of the eyes and the remaining as if they accompanied isolated movements of the hand to the same location. The multiplicative, supra-linear or sub-linear, processes relating effectors and locations to neuron discharges (Chang et al., 2016) might result from gating mechanisms such as those discussed later, in the section handling the sensorimotor decision-making. Alternatively, as considered in the last part of this section, they could result from the coexistence of invariant and effector selective discharges similar to those observed in Meq cells.

The duration of the movement related burst of the majority (31/55=56%) of the Meq neurons we encountered lasted roughly the same whatever the effector executing the movement. Cells that discharge for a long (or short) period of time for saccades also discharge for a long (or short) period of time for hand movements. With three exceptions (cells with saccade related bursts that lasted for a longer period of time than their hand related bursts) the bursts of the remaining Meq cells were brief when they accompanied saccades and prolonged when they accompanied hand movements. This is consistent with the durations of the hand (long) and saccade (short) related bursts of superior colliculus neurons illustrated by Werner et al. (1997a). It is also consistent with the duration of the hand (again long) and saccade (short) related discharges of the PMd neuron illustrated in Fig. 3C of Fujii et al. (2000) and fits the relatively long duration of hand movements (198 ms for 10 degree

movements and 257 ms for 20 degree movements), as well as the relatively short duration of the eye movements (45 ms for 10 degree movements and 58 ms for 20 degree movements). The duration of bursts for coordinated eye hand movements was more difficult to predict. Since saccades precede hand movements by 81 ms on the average, one would expect their eye-hand related bursts to last for at least as long as the time distance between the eye and the hand movement and the duration of the discharge for the hand movement. In fact, it was usually shorter than that of bursts accompanying isolated hand movements and in some cases mixed, in the sense that the cells emitted short bursts for eye/hand movements in some directions, or long bursts for eye/hand movements in other directions.

Does the brain contain additional cells that burst for eye and hand movements besides the Meq cells of the premotor cortex and the aforementioned ones (PEc, PRR neurons) of the superior parietal lobule (Snyder, 2000; Battaglia-Mayer et al., 2001) Previous studies have shown that the visual, saccadic and/or preparatory activity of more than half of the FEF neurons can be modulated by hand position, whether the hand is visible or invisible (Thura et al., 2011). Moreover, the FEF did not show any significant effector preference when fMRI was used to examine if cortical areas would be preferentially activated for saccades or reaches (Levy et al., 2007) while extracellular recordings obtained from primate FEF cells showed at most a modest preference for saccades in a study focusing on tonic delay period discharges (Lawrence and Snyder, 2006). However, to our knowledge there are no descriptions of saccade related FEF neurons discharging phasically for movements of the hand. In our exploration of the FEF region, we encountered only 2 Meq neurons. Their discharge was not remarkable when compared to that of Meq cells of the premotor cortex. They preferred rightward movements of the hand but leftward or downward movements of the eye. The onset of their discharge preceded saccades by about 85 ms and hand movements by about 130 ms and was well correlated to saccade onset in both cells, and to the onset of hand movements in one of them. Actually, it is a subcortical region, the superior colliculus (SC) that contains cells with clear Meq-like responses (Werner, 1993). Werner et al. (1997b) asked monkeys to look at visual targets and after a period of time that could last for hundreds of milliseconds, reach for them. They found 31 cells (about 10% of the total encountered) that resemble our Meq cells, many of them inside the SC and the remaining in the underlying reticular formation. Burst duration depended on the effector executing the movement, and could be short (eye movement) or long (hand movement). Unlike our Meq neurons, 24 of the SC cells responded to visual stimulation as well. The anatomical connections between area 6

and the SC (Leichnetz, 1981; Fries, 1984 ; 1985) could very well underlie the presence of Meq cells in both areas.

Does a single command drive the eyes and the hand?

When looking at an object and manipulating it by hand, eye and hand movements must be coordinated in space and time. Early studies raised the possibility that the two effectors are controlled by a common command (summarized in Kattoulas, 2008). During coordinated movements of the eyes and the hand to the same target, our monkeys first executed a saccade and then a hand movement within a time interval of about 80 ms. Somewhat longer intervals were seen in monkeys executing coordinated saccades and reaches from a central fixation point to a peripheral target in an overlap paradigm (150 ms ; Rogal et al, 1985 or to an odd-colored target among distractors (235 ms in one monkey and 139 ms in another; Song and McPeek, 2009). The extremely short standard deviations these authors reported (1.1 and 1.2, respectively) are indicative of the stereotypical coupling of the two effectors. Intervals roughly equal to 100 ms have been found in human subjects (Herman, 1981 ; Lünenburger, 2000), including a study that, like the present one, required subjects to move a cursor with the help of a hand-held joystick (Boucher et al., 2007). An interval that remained constant at 84 ms for a variety of tasks (step, gap, memory, scanning and antisaccade) was reported by Sailer et al. (2000). Interestingly, Fisk and Goodale (1985) took advantage of the fact that contraversive arm movements start some 40–50 ms after ipsiversive ones and that movements of the right arm precede those of the left, to examine how well the eyes are yoked to the hand. If well yoked then rightward saccades accompanying right-handed ipsiversive reaches should be initiated earlier than right-going saccades accompanying left-handed reaches to the same target. This was indeed the case, the difference being nearly 50 ms ($t = 2.5$, $p < 0.05$), even though in both cases the eyes were moving in the same direction (Fisk and Goodale, 1985).

As we noted in the introduction chapter, numerous studies examined the temporal link between saccades and hand movements focusing on the correlation coefficients of their onset times. The reported correlation coefficients display a remarkable variety. Reported values are sensitive to subject idiosyncrasies as well as task design. For example, in a single human study they were found to range between 0.16 and 0.62 ($p<0.01$) depending on the subject and the test (Boucher et al., 2007). Also, low (or absent) correlation on a trial by trial basis is often due to the severe restriction

of the range of the independent variable (saccade latency) rather than independent commands delivered to the eyes and hand. This could account for the drop in correlation coefficients between saccade latencies and reach latencies from 0.93 (overlap task) to 0.5 (gap task) along with the range of saccade latencies, from 180 - 430 ms in the overlap task to between 100 ms and 170 ms in the gap task (Fischer and Rogal, 1986). The same is true of the insignificant correlation found in the study of Bekkering (1994), which emphasized short hand reaction times, atypically shorter than those of saccades. A considerable reduction of the latency of reaching movements together with that of saccades has been shown in gap trials for human subjects (Lünenburger et al., 2000; Sailer et al., 2000; Gribble et al., 2002) and monkeys (Rogal et al., 1985). Along with these, the relatively high correlations (0.41-0.88) reported by Gribble (2002) for overlap trials dropped to 0.22-0.68 in gap trials ($p<0.01$ in all cases). In turn, correlations increase in tasks that prolong reaction times. Thus, the correlation reported by Sailer (2000) increased for memory (0.68) and antisaccade/antireach (0.74) tasks, which are known to increase saccade latency. Similarly, the low (0.16) correlation between eye and hand latencies reported by Mather and Fisk (1985) increased to 0.4 when the movements were directed to auditory targets, which are known to evoke longer latency movements. The latencies of hand movements and saccades increase together with the correlation between them when the eyes and hand are directed towards somatosensory stimuli (Neggers and Bekkering, (1999)).

In the present study, the correlation coefficient of the relationship between the reaction time of saccades and hand movements on a trial by trial basis was 0.42 in 3540 individual trials of one of our monkeys and 0.49 in 4329 trials of the other (the probability that this might be due to chance was very close to zero in both monkeys). These values agree well with those from two previous reports for the monkey (0.35-0.45, Yttri et al, 2014 ; 0.3 to 0.5, Battaglia-Mayer et al, 2013). Moreover, our study demonstrates that the onset of Meq neuron bursts can be tightly coupled to movement onset and could thus be causally relevant for movement execution. Assuming that two causal chains start from the same central process (e.g., Meq cells) and lead to eye and hand movements, moderate correlations between the onset of the central process and the onset of each effector (in the range of 0.7) would result in correlations between effector onsets that do not exceed 0.5 ($\approx 0.7^2$).

So, the bulk of presently available evidence, including the contents of the present study, indicates that there is a modest but often highly significant correlation between the reaction times of saccades and hand movements of both human subjects and monkeys performing coordinated eye-hand movements to the same target.

Furthermore, the premotor cortex contains Meq cells that discharge for both movements of the eyes and movements of the hand and that the onset of their burst is coupled to the onset of the saccade or the onset of the hand movement and often of both effectors.

Possible role of Meq neurons

It has been argued that rather than drive eye movements, saccadic responses in the premotor cortex provide spatial information (Pesaran et al., 2010) to targets of this area. In a similar vein the presaccadic activity of reach related neurons of the parietal reach region (PRR) was accounted for in terms of a plan that is formed in the PRR carrying the arm to a visual target whenever a saccade is executed to it (Snyder, 2000). In the PRR, Kuang et al. (2016) used reversing prisms to dissociate abstract visual target from physical limb representation and found that neurons in the PRR encode both visual targets and physical movements to them, the latter being the dominant representation. We feel that Meq cells might be more directly involved in the control of eye and hand movements, albeit encoding somewhat more abstract variables, such as an effector independent desired displacement vector anchored on the line of sight. The possibility that premotor cortex neurons encode an abstract retinotopic displacement vector (such as the intended displacement of a cursor on a screen) rather than the limb trajectory or the muscle activations that would bring this about was shown by Shen and Alexander (1997). These authors trained monkeys to move a cursor on a screen with the help of a handheld joystick and manipulated the spatial mappings between joystick and cursor. In the "non-rotated" case forward and rightward movements of the joystick moved the cursor upward and rightward, respectively, while rightward and backward movements of the joystick in the "rotated" case moved the cursor upward and rightward, respectively. Of the directionally tuned PMd cells with premovement-related activity they encountered, there were three times as many that discharged for the intended displacement of the cursor (34/66=51%) as compared to those that discharged for limb trajectory (9/66=14%).

The existence of non-invariant Meq cells may seem at odds with the notion that these neurons encode an abstract version of the intended displacement vector not anchored to the effector employed. It is tempting to speculate that cells with "non-invariant" movement fields would complement the neurons with "effector

invariant" fields, in that both are needed to optimize the choice of effector and the representation of movement metrics. To address this issue, we trained a three layer artificial neural network (ANN) to infer the direction of the movement (to one of eight targets) and the effector executing it (eye, hand or eye/hand) from the average movement related intensity of discharge of Meq cells. The decoding ANN we used is described in the Methods. It reached a high percentage of correct inferences (close to 100% for the effector and more than 90% for the movement direction) when the whole population of our Meq cells (N=55) was used (Fig. 40). To examine the potential contribution of Meq cells with "invariant" movement fields we eliminated a progressively larger number of them from the input layer and retrained the remaining network. We, then, studied the percentage of correct responses it provided, as it attempted to infer the direction of the movement (Fig. 40A, dashed) and the identity of the effector (Fig. 40B, dashed). Similarly, to examine the potential contribution of Meq cells with "non-invariant" fields, we progressively eliminated such neurons from the input of the ANN and examined the percentage of correct responses regarding the direction of the movement (Fig. 40A, solid) and the identity of the effector (Fig. 40B, solid). Elimination was random and was repeated 200 times for each number (n_i) of neurons eliminated. Each one of the 200 resulting ANNs was retrained and their performance was averaged to obtain a value characteristic of networks reduced by n_i neurons. These values are plotted in Fig. 40 as a function of $55-n_i$. The two curves (solid and dashed) remained identical to each other and changed little when the first 7 neurons were eliminated, but diverged when a larger number of cells was removed. Progressive elimination of Meq cells with "invariant" fields led to a significant drop in the number of correct inferences concerning the direction of the movement (Fig. 40A, dashed). On the other hand, progressive elimination of Meq cells with "non-invariant" movement fields led to a significant drop in the number of correct inferences concerning the effector to be used (Fig. 40B, solid). Thus, it would seem that both subpopulations of Meq neurons are needed to minimize errors when programming movements of different effectors to different targets.

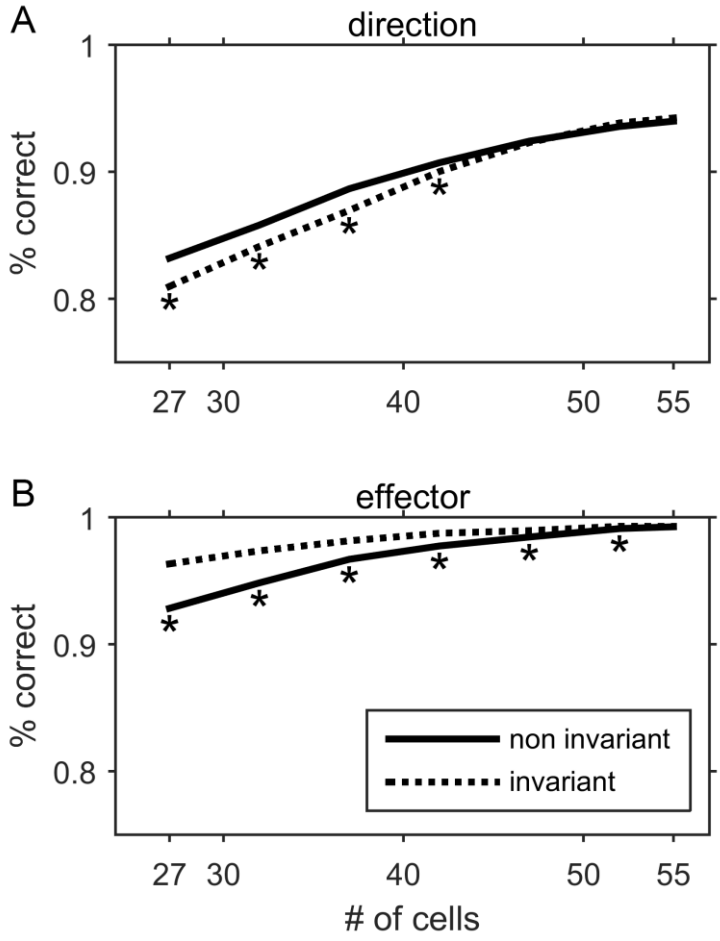


Figure 40. Performance of an artificial neural network in decoding the direction (A) or the effector (B) of a movement from the movement related discharges of Meq neurons. The input layer consisted of a varying mixture of units with effector invariant movement fields and units with effector non-invariant movement fields. The solid line represents the performance of the network when a progressively larger number of non-invariant Meq units are eliminated from the network's input. The dashed line represents the performance when invariant Meq units are eliminated from the input. Asterisks denote statistically significant difference in performance between populations of the same size but different composition (t-test, $p<0.05$).

The notion that Meq cells send the same signal to both eye and hand movers does not imply that the transformations needed to execute hand and eye movements are simple. In fact the opposite is likely to prove true. Firstly, sending the same vector of desired displacement, $\overrightarrow{AB}$, to both eyes and hand suffices only when both effectors start from the same point, A. When the hand movement starts from position C, to obtain the correct vector of desired hand displacement ($\overrightarrow{CB}$) to the same

target, B, one further needs to subtract the vector $\overrightarrow{AC}$ (i.e., the vector of oculocentric initial hand position) from $\overrightarrow{AB}$. This scheme is consistent with the use of an oculocentric frame of reference in the brain to encode arm movements (Batista et al., 1999; Medendorp et al., 2005)). Assuming that it is amplitude control rather than position control (Bock and Eckmiller, 1986; Ghez et al., 1995; Rossetti et al., 1995) that the brain implements in eye-hand coordination, several processing steps are needed to transform the signal carried by Meq cells into that present in α-motoneurons. 1) Gating/decision filters allowing decoupling of eye movement commands from hand movement commands and thus of eye movements from hand movements. 2) Vector decomposition and spatiotemporal transformation to change the labeled line code employed by sensory systems and the hierarchically higher portions of sensorimotor interfaces to the frequency code usually employed by motor systems. 3) Inverse kinematic transformation to obtain the desired changes of joint angles from the desired endpoint displacements. 4) Inverse dynamic transformation to match the frequency content of the signals to the impedance of the effectors, which clearly differ a lot in the case of the eyes and the hands. Processes 2-4 are likely to take place within subcortical structures and some of the mechanisms underlying them have attracted considerable interest in particular as concerns eye movements (e.g., Robinson, 1973 ; Scudder, 1988; Moschovakis, 1994 ; Dean, 1995, 1996 ; Bozis and Moschovakis, 1998 ; Moschovakis et al., 1998 ; Sklavos and Moschovakis, 2002 ; Kardamakis et al. ,2010 ; Joshua et al., 2013). It is worth exploring if gating/decision processes that decouple eye movements from hand movements take place within the premotor cortex.

Study limitations

Our experimental design involved the manipulation of a joystick instead of pointing the targets on a touch screen. Such a setup has been used before (Cisek and Kalaska, 2002) and offers important advantages as the visual confounders are minimal and easy to control and the limb movements are far less strenuous for the animal. However, a consequence of this design is that if the end effector of the movements is considered to be the fingertips rather than the cursor, then the workspace of the eyes is not matching the workspace of the hand.

Saccadic premotor neurons (S cells).

Activation of the premotor cortex for saccades has been shown before (Moschovakis et al., 2004; Savaki et al., 2015). It involves a large part of the superior frontal gyrus straddling the ridge of the cortex (the SEF in the rostral part of the dorsal premotor cortex) and the caudal bank of the arcuate sulcus (in particular its inferior limb). Previous single cell recording experiments have paid particular attention to the former. The pioneering studies of Schlag and Schlag-Rey (1987) documented the existence of saccade related cells in a part of the dorsal premotor cortex (PMd), the supplementary eye field (SEF). Besides illustrating typical examples of SEF presaccadic cells (in Figs. 5A and 6D), Fujii and his colleagues (2002) found cells discharging for saccades in the pre-SMA and the SMA as well as area F2 in the caudal PMd (Fujii et al., 2000), Tanaka and Fukushima (Tanaka and Fukushima, 1998). The present study also found some presaccadic cells (S) in the caudal PMd but many more in relatively ventral parts of the premotor cortex in the caudal bank of the AS. The existence of presaccadic cells of the caudal bank of the AS has been documented before (Figs. 4 - 7 in (Segraves and Goldberg, 1987)). The frequency with which we encountered S neurons in the caudal bank of the AS (27/110=25%) is roughly similar to that reported by Fujii et al. (2002) for the SEF (32%) but considerably higher ($p<0.0001$) than that reported by the same authors for the SMA (6%) and the pre-SMA (10%) or by Fujii et al. (2000) for the caudal PMd (2%). (Fujii et al., 1998).

As with Meq and H neurons but unlike FEF neurons, the responses of S neurons were not lateralized in that their preferred directions were equally likely to be ipsiversive or contraversive. S neurons have somewhat wider movement fields than FEF neurons as shown by the fact that, when fit with a von Mises distribution, average $2/\sqrt{k}$ equals for 135° in the former and 106° in the latter. It should be pointed out that $1/\sqrt{k}$ in the von Mises distribution corresponds to the tuning index (T_d or σ) of previous fits of a Gaussian distribution to the discharge of FEF neurons such that T_d equal to 57.5° (the average found for FEF movement cells; (Bruce and Goldberg, 1985)) corresponds to a value of $2/\sqrt{k}$ equal to 99° a number not too different from the 106° we found in our sample of FEF neurons. Moreover, the duration of the saccade related bursts of S neurons (about 170 ms on average) was longer than that of FEF neurons ($\overline{x}$: 100 ms) and shorter than that of H cells for reaching ($\overline{x}$: 331 ms).

The latency of the bursts of S neurons (54 ms on the average) was shorter than that of Meq cells (mean = 70 ms), but longer than that of FEF neurons (mean = 33

ms). The latter value agrees well with the average latency (28 ms; S.D.: 3.3 ms) determined by Hanes et al. (1995) but is considerably shorter than that reported by other authors (126 ms, (Schall, 1991b); 148 ms, (Segraves and Park, 1993); 150 ms, (Bruce and Goldberg, 1985)). The discrepancy is probably due to methodological differences. We marked the onset of the discharge when the instantaneous firing rate of the cell exceeded the baseline by at least 2 SD. This tended to emphasize the onset of the high frequency portion of bursts. For example, instead of preceding saccade onset by 190 ms, the latency of the neuron illustrated in Fig. 4B of Segraves and Park (1993) would be about 50 ms when measured with our method. On a trial-by-trial basis, the onset of the discharge of S cells was as well correlated to the onset of saccades ($p: < 0.03\text{-}10^{-15}$) as that of FEF cells ($p: < 0.02\text{-}10^{-21}$). This suggests that the saccade responses in the premotor cortex are more directly involved in the control of eye movements than previously thought (Pesaran et al., 2010).

Hand related premotor neurons (H cells).

Given the well documented relationship between the premotor cortex and forelimb movements (e.g., (Caminiti et al., 1991; Raos et al., 2004; Raos et al., 2006)) it is not surprising that we found several neurons (H neurons) that discharge phasically before and during pointing movements of the hand. Cells of the ventral premotor cortex in the caudal bank of the arcuate sulcus were shown before to discharge phasically before and during reaching movements (Godschalk et al., 1981). They have been found in other parts of the premotor cortex as well, namely the SMA, the preSMA and the SEF (Fujii et al., 2002). As with FEF, S, and Meq cells, the phasic discharges of H neurons carried directional information; they preceded hand movements of particular directions and could encode a desired displacement vector (Crammond and Kalaska, 1996) akin to the DV_s vector in the VITE model of Bullock et. al. (1993). This vector represents movements abstractly, as the distance between actual and desired effector position, while other parts of the same model represent movements as desired joint rotations, DV_m. The distinction between DV_s and DV_m reflects known neurophysiology; M1 neurons represent DV_m and DV_s vectors in equal measure while almost all PMv neurons seem to represent the latter (Kakei et al., 2001).

In agreement with previous studies of the premotor cortex (Crammond and Kalaska, 1996; Scott et al., 1997; Ben-Shaul et al., 2003) the preferred directions of

H neurons were uniformly distributed representing both ipsiversive and contraversive movements equally well. The width of the movement field of H neurons ($^{2}/_{\sqrt{k}}$ of the von Mises distribution fit to the intensity of their discharges for movements in several directions) is considerable (mean: 169°). This agrees fairly well to the description of Shimodozono et al. (1997) who reported movement fields of premotor cortex neurons as covering a hemifield. In contrast, the primary motor cortex has narrower movement fields. When fitted with a von Mises distribution the average half-width of the movement fields of M1 cells is 56° (Amirikian and Georgopoulos, 2000). The discharge of H neurons preceded hand movements by 71ms, on the average, and their latency was thus shorter than that of Meq cells (mean = 150 ms). Longer latencies were reported before. Fu et al (1995), Weinrich and Wise (1982), as well as Kakei et al. (2001) reported latencies ranging from 112 ms to 130 ms. However, these studies did not distinguish hand related cells from Meq neurons and because the latter are quite numerous and their latencies are much longer (150 ms), the average latency of the composite population would increase considerably. As expected of cells in an area that is generally considered crucial for the control of hand movements, the onset of the discharge of H cells was well correlated to the onset of hand movements ($p: < 0.05\text{-}10^{-8}$); only 6 H cells failed to display significant correlation between burst onset and hand movement onset.

Although our monkeys used a joystick to direct a cursor towards targets we do not wish to imply that H cells are involved in grasping. Firstly, our monkeys used a combination of arm, forearm and wrist rotations to move the joystick. As a consequence we do not know which part of the forelimb it is that moves because of H neuron discharges. Secondly, only about a fifth of the H cells (N=9) were found in the caudal bank of the AS, while the majority occupied more caudal and dorsal sites in the premotor cortex. The caudal bank of the AS contains much of the area F5 (Raos et al., 2006) and it is for this reason that we mapped it as it provided a landmark that could help us direct recording electrodes. But it also contains cells that discharge for movements other than grasping and controls body segments other than distal forelimb. For example, cells of the PMv in the caudal bank of the arcuate sulcus have been shown to discharge phasically before and during reaching movements (Godschalk et al., 1981) or voluntary movements of the arm, mouth, and head (Graziano et al., 1997). And even though there is a preponderance of distal sites (thumb, fingers), both proximal and distal forelimb movements are evoked from sites in the caudal bank of the arcuate sulcus (Godschalk et al., 1995; Dum and Strick, 2002). Finally, the same region of the PMv in the caudal bank of the AS that projects to the

"hand" area of the primary motor cortex (He et al. 1993) deploys projections to upper cervical segments (He et al., 1993; Dum and Strick, 2002; Martino and Strick, 1987) implying that it could be concerned with the control of proximal and axial body musculature as well.

Clearly, the premotor cortex, which is traditionally associated with skeletomotor control, displays strong saccade related activity. In the same vein, one could ask if the FEF, a cortical region traditionally associated with oculomotor control, exhibits hand related discharges. As noted earlier, hand position has been shown to modulate the activity of more than 50% of the saccade related discharges of FEF cells (Thura et al., 2011). In addition, the human FEF exhibits enough metabolic activity during reach tasks in such a way that no preference between saccades and arm movements is discernible (Levy et al., 2007). In monkeys, FEF visuomovement neurons also discharge similarly in response to eye and hand targets and their discharge diverges only at late delay period where preference for saccades emerges. In contrast, visual FEF neurons exhibit this preference as early as the target is presented, but do have activity for reach targets, nonetheless (Lawrence and Snyder, 2009). On the other hand, Mushiake et. al. (1996) examined the activity of single FEF neurons during saccades, reaches and combined movements of the eyes and hand. Almost all of the cells they studied (n=106) discharged for saccades whether they were followed by hand movements or not. They found only two neurons that discharged during coordinated movements of the eyes and hand. The scarcity of FEF cells responding to hand movements matches our experience. Of the 41 task related neurons that we encountered in the FEF, the only ones sensitive to hand movements were two Meq cells and a single hand related (H) cell.

Other neurons (xS, xH, XOR, AND)

Finally, our sample includes a few cells (N=13) that are best described as logical operators. Some of these neurons discharged for saccades not accompanied by hand movements ($xS: S \wedge \bar{H}$), while others discharged for hand movements not accompanied by saccades ($xH: H \wedge \bar{S}$). A few more discharged if and only if both the eyes and the hand moved to the target (AND), while other cells discharged for movements of either the eye or the hand, but not when eye and hand moved together (XOR). The proportion of these relatively scarce exclusive neurons (xS, xH, AND,

XOR) we encountered in the caudal bank of the AS (6%) is somewhat smaller than the one Fujii et al found in the SMA (19%, $p<0.05$) and the pre-SMA (16%, $p<0.05$) and much smaller than what they encountered in the SEF (37%, $p<1x10^{-7}$) due to the large number of xS cells they found in this region. Their use in a circuit that decides which effector to move and where, is examined in a next section.

Logical operations underlying decision processes

Before embarking on coordinated movements of more than one effector, a subject must decide what to move, where to move it and when to start moving it. Figure 41 is a speculative effort to include the cells presented in this report in a wiring diagram of the movement related flow of information through the premotor cortex. In it, different cell classes were assigned a role in a two-step decision process that leads to effector selection. It starts with the Meq cells whose idealized discharge encodes the vector of displacement as an effector invariant motor command. Their output is routed simultaneously to the AND as well as the XOR neurons, which are mutually antagonistic to implement the first step of the decision process. Higher discharge of AND neurons leads to coordinated movements of the eyes and hand while higher discharges of XOR neurons leads to movements of one of the effectors (hand or eye depending on the outcome of the second decision step). The second decision step is implemented in the mutual antagonism of the xS and xH neurons, which receive excitatory input from the XOR neurons and inhibit the H and the S neurons, respectively. An increased discharge of xS neurons would inhibit H cells and lead to saccades unaccompanied by hand movements whereas increased discharges of xH neurons would inhibit S cells and lead to hand movements unaccompanied by saccades.

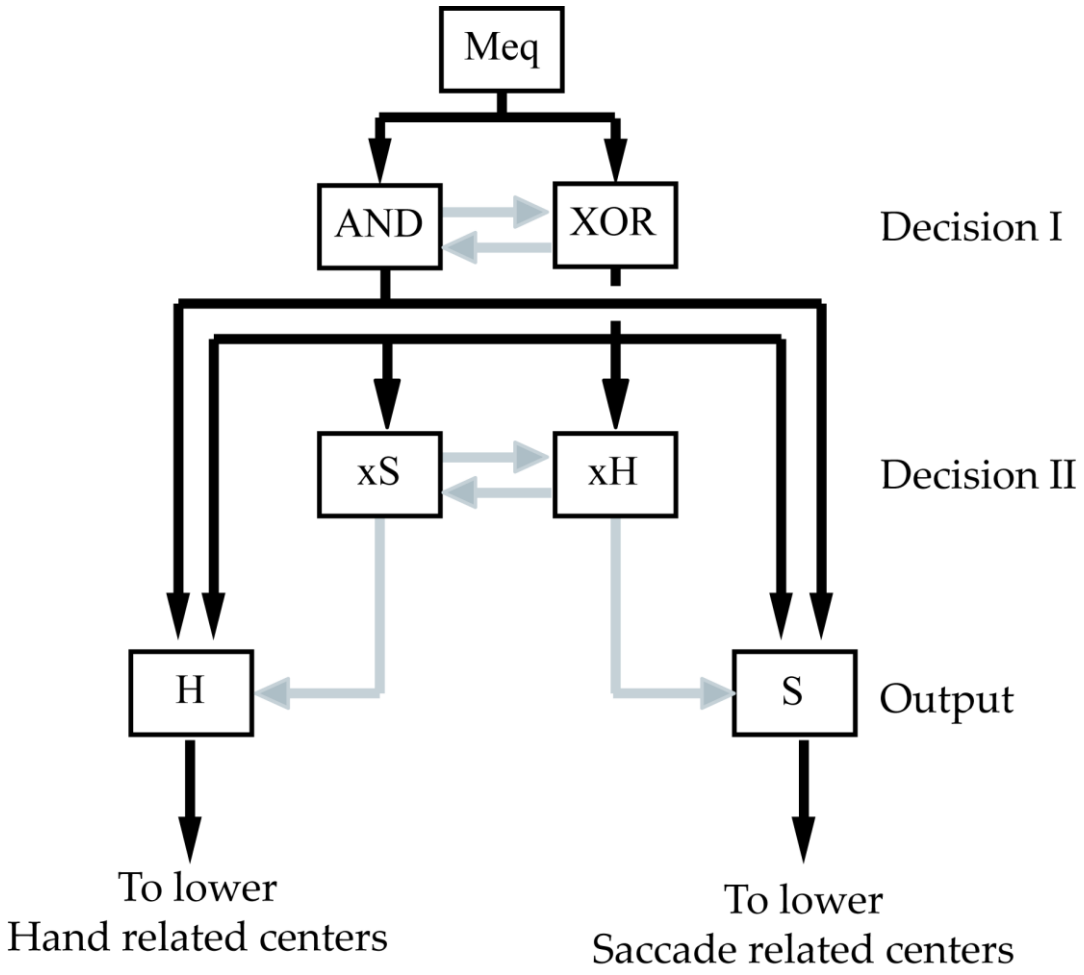


Figure 41. Diagrammatic illustration of the putative relationships between the neuron classes we encountered in premotor cortex. Black arrows mark excitatory connections while gray arrows mark inhibitory ones.

Alternatively, AND, XOR, xS and xH neurons could simply embody the hidden layer of an artificial neuronal network that maps the discharges of Meq neurons onto movements of different effectors in different directions. To explore this issue, we built a three-layer feedforward back-propagation artificial neural network that was driven by Meq units whose simulated movement fields were statistically indistinguishable from those of the Meq cells we encountered. Its input layer consisted of 55 units with Meq like discharges. The activity of each of the input units for 8 positions and 3 effector combinations was drawn from a von Mises distribution whose parameters derived from the movement related discharges of a separate Meq neuron. The network had one hidden layer composed of 100 units. The output layer had 4 units consisting of two pairs of Cartesian coordinates for each one of the two effectors.

So, the intended output was the desired displacement vector of each effector. Unit activations obeyed the expression $tanh(\sum w_{ij}x_j)$ and the connections between them were initially set randomly to values between -1 and 1. Network connections were trained using Matlab's scaled conjugate backpropagation method. 60% of the data were used for the training, 20% for validation and 20% to test the data. To prevent over-fitting, training stopped as soon as the performance in the validation passes started deteriorating.

The output layer encoded the direction of the movement and the effector executing it (eye, hand or both) and could be thought of as information carried by H and S neurons. After the network converged, following its training for 5000 trials, we studied the directional preference of its hidden layer units. Typical examples are shown in Fig. 42 and include AND, XOR, xH and xS units along with Meq, H and S units. In other words, units bearing the characteristics of logical gates are an emergent property of a backpropagation neural network that maps the discharge of Meq units onto the discharge of H and S units. An examination of the weights of the connections established between model units might provide intuition into the precise role that cells of the premotor cortex play in decision processes.

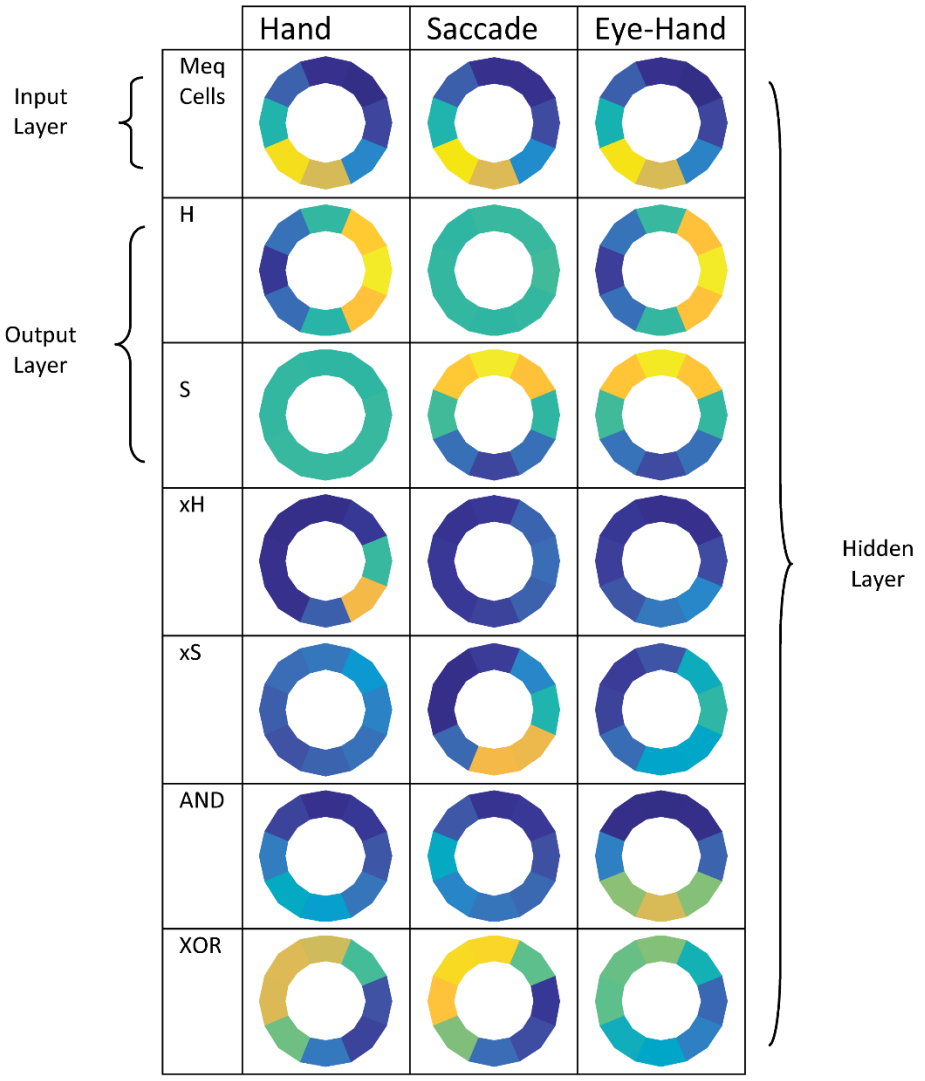


Figure 42. Examples of direction fields of units belonging to a back-propagation artificial neural network that used Meq neuron discharges as inputs and was trained to choose movement effector and movement direction. Each row illustrates the discharge of a single unit for hand (left column), saccade (middle column) and coordinated eye-hand (right column) trials. Yellow shades correspond to higher rates of discharge, green to lower ones and blue to suppression of discharge.

Comparison to past studies on sensorimotor decision making

The decision processes in the sensorimotor systems are often treated within the sequential analysis framework. This entails a decision variable where noisy evidence for or against a specific choice (expressed as the logarithm of the

likelihood ratio) is accumulated over time. At a point, the process is stopped and a commitment to a choice is made (Gold and Shadlen, 2007). One such effort for saccadic movements is the LATER (linear approach to threshold with ergodic rate) model of Carpenter and Williams (1995). In this model the firing rate representing the decision variable rises linearly with a slope derived from a Gaussian distribution. The LATER model specifies the process that commits to a choice; when the firing rate reaches a specific threshold, the decision for a saccade is made. This predicts that the saccadic reaction times would follow a probit distribution. Interestingly, psychophysical data of saccade reaction times give an excellent fit if they are assumed to be derived from two processes, separate for early and late saccades. The LATER model uses a single piece of evidence to determine the slope of the rise of the decision variable. The neurophysiology of the FEF is also consistent with this model. Hanes and Schall (1996) showed that the rate of growth of the presaccadic discharge of the majority of FEF presaccadic cells (22 out of 25) is inversely proportional to the latency of the movement executed.

On the other hand, in sequential analysis implementations for perceptual decisions and target selection, the rise of activity is due to the integration of information over time (Usher and McClelland, (2001); Mazurek et al, 2003 ; Schall et al, 2011). Those decision processes also involve competition between numerous choices. This competition might be realized with no interaction between the processes, where the winner is simply the one that reaches the threshold first, but models implementing lateral inhibition between the processes, winner-take-all mutual inhibitory connections and gating mechanisms have been shown to perform well and in agreement to behavioral data (Schall et al., 2011).

Decision circuits can be biophysically implemented in recurrent neural networks as well (Wang, 2008). Mutual inhibition and recurrent excitations between the units representing the competing processes create the attractor dynamics that from the decision landscape. Sensory evidence reshape the basins of attraction of this landscape and skew the decision probabilities accordingly. As noted previously, mutually inhibitory connections with bistable dynamics have been added as components to accumulator models (eg (Mazurek et al., 2003) and (Schall et al., 2011)). Kopecz and Schoener's (1995) dynamic field network for saccade target selection employs a connection topography where a unit representing a movement direction interacts laterally by exciting units of neighboring directions and inhibiting units of distant ones. This arrangement averages the two competing motor plans, if they are similar enough. However, if they are distant, the bistable interactions force the

domination and selection of just one of them. Cisek's (2007) approach shares common ground with Kopecz and Schoener's perspective, but also brings forward Gibson's notion of affordances (1977) where perception and action are intertwined in an assortment of motor options that are relevant to the agent's current ecological environment. In Cisek's proposal affordances are represented by a leaky integrator towards a threshold where similar actions excited each other and dissimilar actions were mutually inhibited. While his proposal implemented the affordances as direction of action, the concept is broad enough to imply actions involving multiple effectors or combinations of them.

Such lateral interactions among the decision processes of different effectors were suggested by Dean et al. (2011). They studied the reaction time correlations of saccades and reaches to distinct and asynchronous sensory signals. The correlations were positive for synchronous movements (~0.4) but could obtain negative values when the stimuli were asynchronous. Modeling the timing of the onsets with leaky integrator accumulators does account for the positive correlations when both processes have a common gain or a common input (common noise source). However, lateral interactions between the two processes are required to account for both positive and negative correlations.

The termination of the decision process and the initiation of the movement in race models is straightforward; the first action that reaches the threshold is selected. Wang's (2008) recurrent network employ a separate termination mechanism that forces the commitment to a choice and pins down the basal ganglia as a possible locus of this step. Schall et al (2011) include in some of their accumulator models a gating mechanism. This, in effect, splits the decision process into two parts where an earlier decision on e.g. visual target selection acts permissively for the evidence accumulation process of the movement planning to start. They name inhibitory interneurons in the frontal eye fields, fixation neurons in the frontal eye fields or interactions of the frontal eye fields with the basal ganglia as potential realizations of this gating operation. The mechanism we illustrate in Fig. 39 suggests that such gating operation for effector selection could take place in the premotor cortex and permits an effector invariant target selection to proceed into an effector specific motor plan. By the time S neurons start emitting the high frequency portion of their discharge the subject has decided which effector to use (eyes). Since, as shown here, this precedes the onset of the burst of FEF neurons, effector selection could precede the onset of the race towards the start of the movement, a conclusion

consistent with the demonstration that a motor goal is formed only after an effector is selected for action (Bernier et al., 2012).

Anatomic relationships in support of the proposed role for the PM

To some extent the sort of decision process that can be implemented in the premotor cortex depends on the connections between the neurons entrusted with its implementation. With the possible exception of some long range projections of PMv cells (Segraves and Goldberg, 1987), there is no information about the projections of functionally identified cells of the premotor cortex. Known anatomy allows us at most an approximate list of the regions that influence and/or are influenced by the caudal bank of the AS. Given the fact that the onset of the phasic, saccade related discharge of S cells precedes, on average, that of FEF cells the former is unlikely to be generally due to the latter. On the other hand, since some S neurons display shorter latencies it is reasonable to ask if the FEF projects to the caudal bank of the AS. In fact, the existence of such a projection is controversial. Injection of WGA-HRP into area 45 (overlying some of the anterior wall of the inferior limb of the AS and the neighboring exposed convexity) labeled terminal in the inferior premotor area, both inside the posterior wall of the AS and the exposed convexity behind it (Arikuni et al., 1988) and FEF cells were retrogradely labeled following HRP injections into the post-arcuate cortex (Arikuni et al., 1980). Also, Stanton et al. (1993) found a projection, albeit modest, to area FCBm of von Bonin (1947) (in the deep posterior wall of the AS) and a small number of terminals were seen in the vicinity of the spur after injection of WGA-HRP in the physiologically defined FEF (Huerta et al., 1987). Labeled neurons have been found in the FEF by some authors (Godschalk et al., 1984; Barbas and Pandya, 1987; Stanton et al., 2005) but not by others (Matelli et al., 1986; Kurata, 1991) following HRP injections in the caudal bank of the AS.

Although early studies indicated that the FEF receive input from area 6 (Walker, 1940; Pandya and Kuypers, 1969), the reverse connection between the premotor cortex and the frontal eye fields is also controversial. Matelli et al. (1984) did not find a projection of the caudal bank of the AS to the FEF. Also, no major projection from the premotor cortex to the FEF was found after injections of ^{3}H-proline in the caudal bank of the AS (Barbas and Pandya, 1987) while a few cells of the premotor cortex were retrogradely labelled after HRP injections in area 8 (Barbas and Mesulam, 1981). On the other hand, retrogradely labelled cells have been seen in the posterior bank of the AS after tracer injections in the FEF (Jacobson and Trojanowski, 1977; Huerta et al., 1987; Stanton et al., 2005).

A projection of the premotor cortex, and in particular the caudal bank of the AS, to the superior colliculus (SC) has been demonstrated with retrograde (Leichnetz et al., 1981; Fries, 1984; 1985) and anterograde (Borra et al., 2014) tract tracing. It is therefore not surprising that SC neuron discharges closely resemble those of the caudal bank of the AS. Besides saccade related cells (Wurtz and Goldberg, 1972; Sparks, 1975; Moschovakis et al., 1988), the SC contains cells discharging for hand movements (Werner et al., 1997b) as well as cells that, akin to Meq neurons, discharge for saccades and hand movements (Werner et al., 1997a). The projection of the premotor cortex need not relay only hand related signals. Some of the neurons of the caudal bank of the AS that were antidromically identified following electrical stimulation of the SC displayed presaccadic discharges (Segraves and Goldberg, 1987).

Given the strong presence of saccade related signals in the caudal bank of the AS and its projections to the SC it is reasonable to ask if its electrical stimulation of the caudal bank of the AS would lead to saccade generation.

Microstimulations

Our microstimulation experiments demonstrated that saccades can be evoked from the premotor cortex in and behind the caudal bank of the AS and its spur. This is 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 motorneurons (Moschovakis et al., 2004), its projection to the superior colliculus (Leichnetz et al., 1981; Fries, 1984; 1985; Segraves and Goldberg, 1987; Borra et al., 2014) and the FEF (Jacobson and Trojanowski, 1977; Huerta et al., 1987; Stanton et al., 2005) as well as the herein demonstrated phasic, saccade related discharges of the neurons it contains.

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 in the same subjects to contain neurons discharging for grasps and object observation, identified for the needs of a different study (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. The two major deficits arising from lesions of the posterior bank of the AS lend support to such a cautious interpretation of the data.

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 a musculoskeletal deficit manifested in clumsy use of the fingers, difficulty in grasping food with the mouth (Rizzolatti et al., 1983) and impaired hand shaping for object grasping(Fogassi et al., 2001).

Rostrally, the saccade evoking post-arcuate region overlapped the smooth pursuit area and more rostrally still, it neighbored a part of the FEF responsible for saccades with small horizontal components. Several details of this description agree well with previous work. Sites evoking smooth pursuit eye movements have been shown to occupy part of the posterior bank of the AS next to the small saccade region of the FEF (Gottlieb et al., 1993) and the same is true of area F5 which contains neurons discharging for grasps and object observation (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. The region we studied 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 their region was 5 mm ventrolateral to the spur and at least 3 mm behind the arcuate sulcus from which it is separated by an area representing the arm (Fujii et al., 1998). In contrast, we studied a region that lies in 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 sites likely to correspond to those studied by Fujii and his colleagues.

The characteristic vectors of the saccades we evoked from post-arcuate sites clearly differ from those of FEF sites. Those of the FEF were contraversive whereas the characteristic vectors of post-arcuate evoked saccades 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. In contrast to FEF presaccadic sells that generally prefer contraversive saccades, the on directions of post-arcuate cells are not lateralized. There are as many post-arcuate 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%) for post-arcuate evoked ones. Also in agreement with previous observations (Fujii et al., 1998), post-arcuate evoked saccades were found to be 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 (Moschovakis et al., 1998; Kardamakis et al., 2010)).

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 757 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 590 deg/s and 544 deg/s to fit ($R^2 = 0.82$ 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. For example, inhibition of omnipause neuron (OPN) discharges are expected to do so because they intervene with the normal build-up of activity of the resettable integrator (Moschovakis, 1994). Consistent with it, OPN lesions in monkeys have been shown to reduce saccadic eye velocity (Kaneko, 1996). 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 post-arcuate cortex (Fig. 27, asterisks), have been shown to participate in large eye-head gaze shifts (Freedman and Sparks, 1997). On the other hand there is no reason to think that the post-arcuate cortex is more intimately connected to the OPNs or that it is more directly related to head movers than the FEF. In fact, presently available evidence supports FEF rather than premotor projections to

the OPN region (Stanton et al., 1988) and the same is true of their involvement in eye-head movements (Knight and Fuchs, 2007; Monteon et al., 2010). Besides saccades, smooth pursuit, eye-hand coordination and grasping movements the posterior bank of the AS has been implicated in the execution of blinks (Amiez and Petrides, 2009). In turn, blinks have been shown to interrupt the discharge of OPNs (Schultz et al., 2010) and slow down saccades (Rottach et al., 1998; Goossens and van Opstal, 2000). Engagement of the mechanism responsible for their generation could thus account for the lower velocity of saccades electrically evoked from the post-arcuate cortex. It should be noted that the effect is rather subtle, consistent with the paucity of overt blinks in response to the electrical stimulation of the post-arcuate cortex.

In conclusion, electrical stimulation of the premotor cortex in the caudal bank of the AS and its spur evokes saccades with ipsiversive characteristic vectors. In addition, saccades evoked from the post-arcuate cortex are slower than visually guided saccades and saccades evoked from the FEF. Consistent with the notion that this area can produce saccades, is the presence of numerous cells that exhibit phasic activity before saccades. These cells have preferred directions that can be ipsiversive or contraversive and initiate their movement related discharge earlier than their counterparts in the FEF. This evidence demonstrates that saccade related discharges in the premotor cortex are unlikely to be merely a copy of FEF motor commands. Moreover, several of the saccade related cells of the premotor cortex also discharge for movements of the hand. The coexistence of effector invariant and effector specific signals in the premotor cortex suggests that this is a locus where movements are encoded in an abstract and effector-neutral manner, as well as a locus involved in the decision processes leading to effector selection.

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