

Preparatory Activity in Premotor and Motor Cortex Reflects the Speed of the Upcoming Reach

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Churchland, Mark M., Gopal Santhanam, and Krishna V. Shenoy. Preparatory activity in premotor and motor cortex reflects the speed of the upcoming reach. *J Neurophysiol* 96: 3130–3146, 2006. First published July 19, 2006; doi:10.1152/jn.00307.2006. Neurons in premotor and motor cortex show preparatory activity during an instructed-delay task. It has been suggested that such activity primarily reflects visuospatial aspects of the movement, such as target location or reach direction and extent. We asked whether a more dynamic feature, movement speed, is also reflected. Two monkeys were trained to reach at different speeds (“slow” or “fast,” peak speed being ~50–100% higher for the latter) depending on target color. Targets were presented in seven directions and at two distances. Of 95 neurons with tuned delay-period activity, 95, 78, and 94% showed a significant influence of direction, distance, and instructed speed, respectively. Average peak modulations with respect to direction, distance and speed were 18, 10, and 11 spikes/s. Although robust, modulations of firing rate with target direction were not necessarily invariant: for 45% of neurons, the preferred direction depended significantly on target distance and/or instructed speed. We collected an additional dataset, examining in more detail the effect of target distance (5 distances from 3 to 12 cm in 2 directions). Of 41 neurons with tuned delay-period activity, 85, 83, and 98% showed a significant impact of direction, distance, and instructed speed. Statistical interactions between the effects of distance and instructed speed were common, but it was nevertheless clear that distance “tuning” was not in general a simple consequence of speed tuning. We conclude that delay-period preparatory activity robustly reflects a nonspatial aspect of the upcoming reach. However, it is unclear whether the recorded neural responses conform to any simple reference frame, intrinsic or extrinsic.

INTRODUCTION

Voluntary movements are believed to be “prepared” before they are executed (Day et al. 1989; Ghez et al. 1997; Keele 1968; Kutas and Donchin 1974; Riehle and Requin 1993; Rosenbaum 1980; Wise 1985). An important line of evidence comes from tasks where a temporal delay separates an instruction stimulus from a subsequent go cue. At the behavioral level, reaction times (from the go cue until movement onset) are shorter after an instructed delay, suggesting that some time-consuming preparatory process is given a head start by the delay (Churchland et al. 2006; Riehle and Requin 1989; Riehle et al. 1997; Rosenbaum 1980). At the cellular level, neurons in a number of brain areas, including dorsal premotor cortex (PMd) and primary motor cortex (M1), show changes in activity during the delay (Godschalk et al. 1985; Kurata 1989; Riehle and Requin 1989; Snyder et al. 1997; Tanji and Evarts

1976; Weinrich et al. 1984). This “preparatory” activity typically shows tuning for the instruction. Its state predicts reaction time (Bastian et al. 2003; Churchland et al. 2006; Riehle and Requin 1993), and its disruption increases reaction time (Shenoy and Churchland 2004), arguing that it is indeed related to motor preparation.

In understanding how movements are prepared, it seems important that we determine which reference frames describe the neural responses at each temporal, anatomical, and functional stage. (By reference frame we simply mean a low-dimensional set of variables, spatial or otherwise, on which neural activity is posited to depend in some straightforward fashion.) Such knowledge should also have immediate practical significance, given recent efforts to guide motor prostheses using preparatory activity (Musallam et al. 2004; Santhanam et al. 2006; Shenoy et al. 2003b). It is often assumed that reach preparation occurs in a predominantly spatial reference frame (e.g., van Beers et al. 2004). In support, preparatory activity in PMd is tuned for target direction and distance (Kurata 1993; Messier and Kalaska 2000; Riehle and Requin 1989) and is more closely tethered to the visuospatial location of the target than to the direction of the reach (Shen and Alexander 1997b). Recent work has asked whether the relevant spatial reference frame translates with the hand, eye, or both (Nelson et al. 2005). Yet some results suggest that PMd/M1 preparatory activity might not obey a simple spatial reference frame. PMd activity can depend on factors other than target location, including the type of grasp (Godschalk et al. 1985), the required accuracy (Gomez et al. 2000), reach curvature (Hocherman and Wise 1991), and (to some degree) force (Riehle et al. 1994).

Our goal was to determine whether preparatory activity in PMd and M1 reflects a nonspatial aspect of the upcoming reach: its speed, instructed by target color. We found that preparatory activity showed a strong influence of instructed speed comparable to that for direction and distance. Furthermore, both direction and distance tuning could vary with the instructed speed. These results *may* indicate that reach velocity is directly “represented” during motor preparation. However, it is at least as likely that the observed tuning relates to factors that correlate with reach velocity (e.g., initial acceleration or muscle co-contraction). A lack of invariant tuning for any of the tested parameters, together with a high degree of heterogeneity across neurons, question the idea that preparatory activity obeys *any* clear reference frame. Preliminary reports of

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this data have appeared previously (Churchland and Shenoy 2003; Shenoy et al. 2003a).

METHODS

Task design and training

Animal protocols were approved by the Stanford University Institutional Animal Care and Use Committee. Our basic methods have been described previously (Churchland et al. 2006). Briefly, two adult male monkeys (*Macaca mulatta*, ~10 kg) sat in a customized chair with head restraint and performed the task on a fronto-parallel screen. The hand and eye were tracked optically (accuracy of 0.35 mm and ~1°, 60 and 240 Hz). Figure 1, *A* and *B*, illustrates the task structure. Each task trial began with the appearance of a 12-mm-diam central spot. The target appeared once this was touched and held for 400–500 ms. During the subsequent (randomized) 400- to 800-ms delay period, the target “jittered” slightly (2 mm SD). If the hand moved during this time, the trial aborted and the target swiftly “flew” off the display. Monkeys rapidly learned that the jittering target could not be struck, and the hand was typically held very steady during the delay period. Most experiments included occasional (1 in 5) short delay-period (30–330 ms) nonanalyzed “catch” trials, intended to ensure attention throughout the delay. When target jitter ceased and the central spot disappeared (the go cue), monkeys were required to reach to the target. Allowable reaction times were 150–500 ms. End-point accuracy requirements varied with monkey/target distance (see Fig. 3). Juice reward was delivered after the target was held for 300 ms.

Monkeys were trained to reach at different speeds, with green and red targets instructing “slow” and “fast” reaches. The central spot received the same color coding. For fast reaches, peak reach velocity had to exceed a threshold, while for slow reaches peak velocity had to fall within a window (see Fig. 2). To aid training, we introduced the following task features. For red targets, overly-slow reaches were detected on-line and the target immediately flew off the screen as described in the preceding text. For overly fast reaches to green targets, the reward was still delivered but was delayed in proportion to the error. These aspects of the task were trained after performance was already excellent for the simple delayed reach task. Speed training was initially performed at an intermediate target distance, with the velocity thresholds set to split the range of natural velocity variability. When introducing other target distances, no criteria were initially set, allowing us to observe the natural progression of peak velocity with distance for the two target types (e.g., Fig. 2*D*). Thresholds (colored bars) were set based on these observations. Once training was complete, most trials (94 and 92% for monkeys *A* and *B*) satisfied the velocity constraints, something that would take practice for a human to equal.

Although success was determined by peak velocity, there is no reason to believe that monkeys understood this (they may have focused on controlling reach duration). A variety of other factors, some measurable (e.g., peak acceleration, patterns of muscle activity), some not (e.g., effort) also varied (or presumably varied) between instructed speeds. For example, achieving a given endpoint accuracy is presumably harder for the instructed-fast condition (Fitt’s Law), and

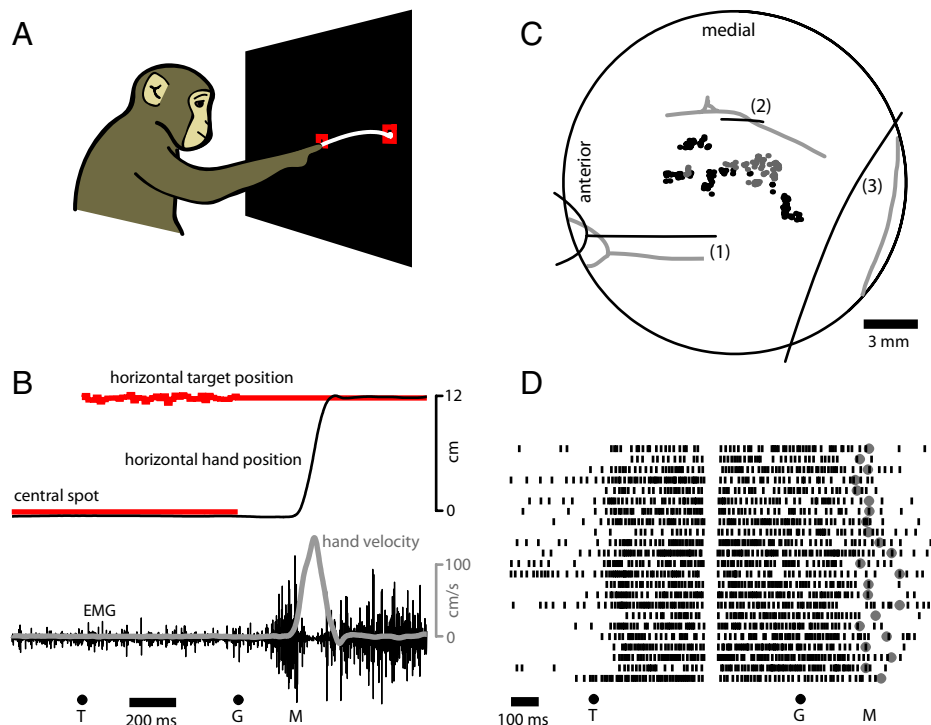


FIG. 1. Illustration of the task, behavior, and neural recordings. *A*: monkeys sat in a primate chair ~26 cm from a fronto-parallel display. Movements began and ended with the hand touching the display. The hand was a few mm from the screen while in flight. The white trace shows the reach trajectory for 1 trial. *B*: time line of the task and behavior for the same trial. T, target onset; G, go cue, and M, movement onset. Horizontal hand (black) and target (red) position are plotted (*top*). The target jittered on first appearing and ceased at the go cue. *Bottom*: gray trace plots hand velocity (computed in the direction of the target), superimposed on the voltage recorded from the medial deltoid (arbitrary vertical scale). Traces end at the time of the reward. Data are from monkey *A* in a session focused on electromyographic (EMG) recordings. *C*: locations of recording sites (1 dot/neuron) for monkey *A* (gray dots) and *B* (black dots). A small amount (0–0.3 mm) of random displacement has been added to the dots to make it clear when multiple recordings were made at the same location. The large circle outlines the limits of the implanted cylinder. Lines give the location of the spur of the arcuate sulcus (1), the precentral dimple (2), and the central sulcus (3). For monkey *B* (black lines), these are estimated via MRI. For monkey *A* (gray lines), measurements were made at autopsy and agreed closely with the prior estimates from MRI (not shown). *D*: responses of 1 example neuron (B24). Rasters (on tick per spike) are shown for the 23 trials in which a red (fast) target was presented 12 cm away at 45°. Gray circles, movement onset for individual trials. For the left (right) side of the plot, data are time-locked to target onset (the go cue). The vertical band with no spikes corresponds to the split between these analysis epochs.

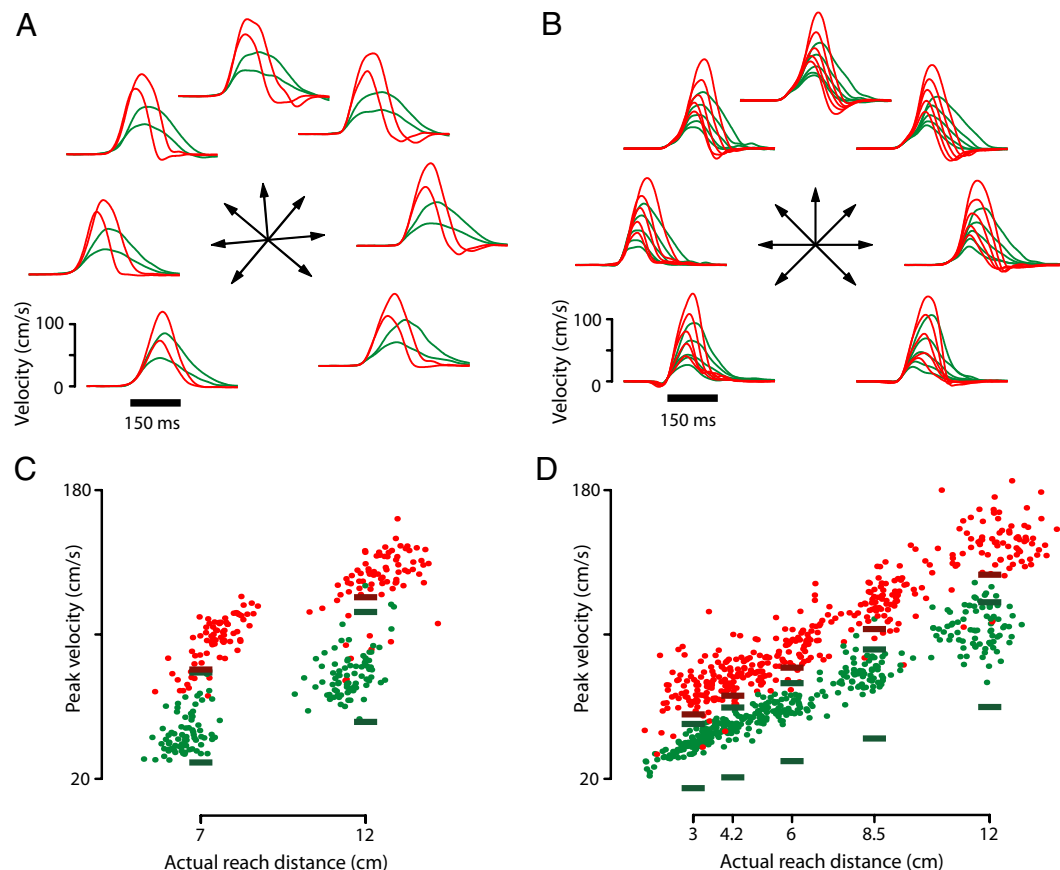


FIG. 2. Analysis of reach velocity. Red and green traces/symbols plot data for fast and slow reaches to red and green targets. *Left and right*: data for monkeys A and B, respectively. Hand velocity (and its peak) were computed in the direction of the target, after low-pass filtering (25-Hz cutoff) the hand-position signal. To allow a fair report of behavior, all analyses include all recorded trials (including endpoint and peak-velocity errors and catch trials). A: mean hand velocity as a function of time. Data for each target direction form a subpanel. Within these, the 4 traces correspond to the 2 instructed speeds and 2 target distances (7 and 12 cm). Means are locked to movement onset with ~ 11 trials/condition. Data are from the same trials as the neural data in Fig. 4, A and B. B: similar plot but for monkey B. This monkey was tested using both direction and distance series. To allow complete documentation of behavior across all 7 directions and 5 distances, the presented data were collected in a special session devoted to behavior, made just before recording began (~ 11 trials/condition). C: peak hand velocity vs. reach distance (309 trials), same dataset as in A. The 4 clusters correspond to the 2 target distances and the 2 instructed speeds. Data are collapsed across directions. Bars (dark green and dark red) plot the acceptance criteria for reward for the red and green targets. Reach distance was computed as the distance between hand position at the time of the go cue and hand position 50 ms after the reach ended. To allow the software to react appropriately, peak reach velocity was estimated on-line but was very similar if computed off-line after filtering. D: similar plot but for the dataset in B (774 total trials).

this could certainly influence neural responses (Gomez et al. 2000). In general, we do not wish to argue that an observed influence of instructed speed should be attributed to reach velocity per se. Factors that correlate with reach velocity (including muscle activity) are also strong candidates. That said, with regards to the speed/accuracy tradeoff, we did make a rough attempt to counterbalance the design across the two monkeys. For monkey A, we employed forgiving acceptance windows that were larger for the fast reaches. For monkey B, windows were tighter and did not depend on instructed speed (see Fig. 3, C and D). We also note that the most challenging aspect of training was the association between color and speed. Once this was understood, monkeys typically showed high levels of endpoint accuracy for both instructed speeds.

Trial types and datasets

We collected two types of datasets. The direction series used two target distances (7 and 12 cm for monkey A; 5 and 12 cm for monkey B) and seven directions (5, 50, 95, 140, 185, 230, and 320° for monkey A; 10, 55, 100, 145, 190, 235, and 325° for monkey B). Seven (rather than 8) directions were used because there was always one target location that the monkey could not see through his arm. For each monkey, the pattern was rotated slightly to ensure that the arm did not

have to be moved to see the targets flanking the $\sim 270^\circ$ missing direction. The distance series used five distances (3, 4.2, 6, 8.5, and 12 cm) in the preferred and anti-preferred direction of each neuron, estimated using a cursory direction series. If the anti-preferred direction was near 270° , that target was moved slightly to one side or the other. Distance series were collected only for monkey B and used a slightly longer range of delay-period durations (500–900 ms). Trials were always presented using a randomized-block design with any failed trials re-presented at a random time before proceeding to the next block.

Neural and EMG recordings

Our methods for neural recordings are reported in Churchland et al. (2006). Briefly, monkeys were implanted with a cylinder located according to a prior MRI scan. Using single hydraulically driven electrodes, single units were isolated manually, and electrode position was adjusted when needed to maintain isolation. Recordings were made from caudal PMd and M1 (Fig. 1C). We avoided rostral PMd, from which eye movements can be evoked (Fujii et al. 2000) and which projects less densely to M1 and the spinal cord (Dum and Strick 2005). A modest number of sites were recorded in the deeper portions of M1 (i.e., in the sulcus below the cortical surface). Microstimulation

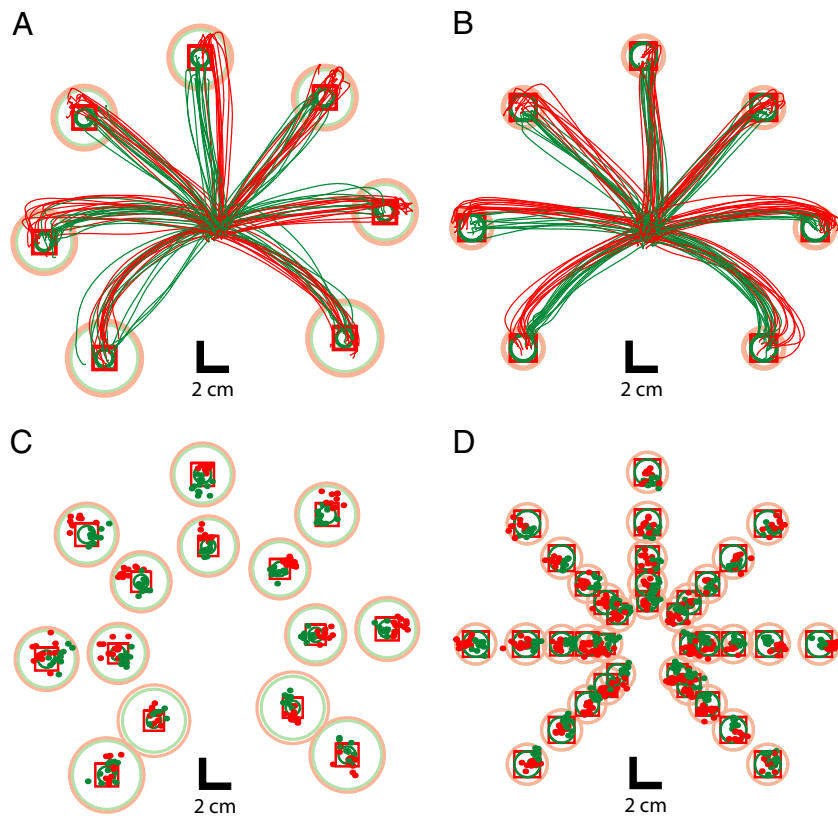


FIG. 3. Reach trajectories and endpoints. *Left and right*: data for *monkeys A and B*, respectively. Red and green traces/symbols correspond to the instructed-fast and instructed-slow conditions, respectively. Data are from the same datasets as Fig. 2 and are plotted for all saved trials (including any misses or failures). *A*: reach trajectories for *monkey A* for the more distant (12 cm) targets. Target locations/dimensions for the 7 directions are shown by the solid red squares and green circles. The larger light circles plot the acceptance windows for reach endpoint. Reach trajectories are plotted from the time of the go cue until 50 ms after the target was touched. *B*: similar plot for *monkey B*. End point accuracy was more tightly enforced than for *monkey A* and was the same for red and green targets (light red circles plot the acceptance windows). *C*: reach endpoints for all targets for *monkey A*. The radii (in mm) of the targets (acceptance windows) for the 2 distances were 5 (19) and 6 (21) for the instructed-slow condition and 7 (21) and 8 (22) for the instructed-fast condition. Reach endpoints were computed 50 ms after the reach ended. Results were essentially identical when measuring 200 ms after (not shown). *D*: similar plot but for *monkey B*. Target (acceptance window) radii were 7 (12), 8 (13), 8 (13), 9 (14), and 9 (14) mm for the 5 distances and were the same for the 2 instructed speeds. The acceptance windows were sometimes increased for sessions or locations (usually downward) where the monkey had difficulty with the required accuracy. The effect of providing such relief was typically that performance improved rather than degraded further.

(biphasic pulses, 333 Hz, 57 ms) applied to the recorded zones caused movements of the forelimb, most often originating from the shoulder. Infrequently, microstimulation evoked movement of both the fore and hindlimb, or of the trunk. Using the same high-impedance electrodes as for recording, thresholds varied from $<25 \mu\text{A}$ in M1 to $>200 \mu\text{A}$ in PMd. EMG activity was recorded during separate dedicated sessions, as described in Churchland et al. (2006). EMG traces were differentiated to remove any baseline that survived filtering, rectified, and smoothed (25 ms SD Gaussian). The mean was then taken across trials and for some analyses across time.

Criteria for inclusion of neural data

We recorded responses from 189 neurons: 138 for the direction series task (64 for *monkey A* and 74 for *monkey B*) and 51 for the distance series task (all from *monkey B*). Rather than recording from as many neurons as possible, we chose to characterize the activity of each neuron as completely as possible, using a moderately large number of conditions and trials/condition. The mean number of trials/neuron was 381 for the direction series and 280 for the distance series. In terms of total trials collected, our dataset is comparable to that of other studies with very high neuron-counts (e.g., Moran and Schwartz 1999b collected data from 1,066 neurons with 40 trials/neuron).

Some selection occurred during experiments when recordings of nonresponsive neurons were aborted. A further selection was performed to concentrate analyses on neurons with tuned delay-period activity. For neurons that showed subsequent movement-related activity, we also insisted that delay-period activity be reasonably robust in comparison. For neurons with strong movement-related activity but weak delay-period activity, the latter could in principle be related not to motor preparation but to small changes in muscle tone. This is not a large concern, as EMG recordings indicated little or no change in muscle activity during the delay. However, in the interests of being conservative we wished to exclude such neurons from analysis. Our

criteria for inclusion were thus 1) that there was at least one condition (target location/instructed speed) with a delay-period firing-rate change >5 spikes/s relative to the 300 ms “baseline” period before target onset, 2) that delay-period firing rates varied significantly across conditions ($P < 0.05$, single-factor ANOVA), and 3) that the maximum delay-period modulation was $>20\%$ of the mean peak response around the time of the movement. These criteria insist only that delay period activity be present, tuned in some way, and reasonably robust compared with subsequent movement-related activity. For the direction and distance series, 95/139 and 41/51 neurons satisfied these criteria. All subsequent analyses are restricted to these subsets. If we define cylinder zero (approximately the middle of the precentral dimple) to be (very roughly) the PMd/M1 border, then 53% (47%) of analyzed neurons were recorded from PMd (M1).

Data analysis and statistical tests

Trials were analyzed if the target was hit accurately and held until the time of reward (typically $\sim 98\%$ of saved trials). Trials aborted because the hand moved during the delay (or never moved) were not saved but comprised at most a few percent of trials. Violations of the peak hand-velocity constraints were more common (6–8%) but usually involved peak velocity being only slightly too fast or too slow. We saw no compelling reason to exclude such trials from analysis. The small errors in question occurred after the analyzed epoch (the delay) and probably did not reflect a lack of effort/preparation on the part of the monkey but rather the challenging nature of the task. Such trials formed a continuum with correct behavior (indeed, they often resulted in only a slight delay in the reward, see preceding text). We have recomputed key analyses (e.g., the modulation strength for instructed speed) excluding peak-velocity violations, and effects are not reduced (if anything, effects become very slightly stronger).

Plots of mean firing rate versus time were made by convolving spike trains with a Gaussian (25 ms SD) and averaging across trials. Quantitative analyses employed the mean delay-period firing rate,

from 50 ms after target onset until 50 ms after the go cue. Because the delay period was variable and firing rates could be nonstationary for some neurons (e.g., Fig. 4C), using the entire delay period for each trial introduces a source of variability that could reduce statistical power. However, the alternative—analyzing only the initial part of the delay (up to the minimum)—also incurs a loss of statistical power due to the shorter time over which noisy spike-trains are averaged. In our experience, the potential for a loss of statistical power is usually greater for the latter method, and thus we analyze the entire delay for every trial. Note that there is no potential for artifact, as the delay duration was randomized in the same way for every condition. We have also repeated a number of analyses using the “minimum-delay” method. Statistical power is slightly diminished but effect magnitudes are very similar.

We define the “modulation strength” as the maximum modulation caused by a given factor, across all values of the other factors. In the case of direction, we took the difference in firing rate between the

directions evoking the largest and smallest responses. This was done separately for each distance and instructed-speed. We then took the maximum effect across all distance/speed combinations

$$\max_{\text{dist,spd}} (\max_{\text{dir}} (f_{\text{dir,dist,spd}}) - \min_{\text{dir}} (f_{\text{dir,dist,spd}})) \quad (1)$$

where $f_{\text{dir,dist,spd}}$ is the mean delay-period firing rate for a given direction, distance, and instructed speed. The modulation strength for distance and speed were defined analogously.

For direction series, the preferred direction (PD) of each neuron was estimated separately for each distance and instructed speed. Mean firing rate was plotted against target direction, and data were fit with a cosine (free parameters were phase, amplitude, and DC offset). The peak, θ_{pref} , was taken as the PD. Note that, for a cosine fit, there is no bias created by the lack of the eighth (downward) direction. A bootstrap procedure was used to compute the sampling distribution of θ_{pref} , expected given measurement error. For each target direction we

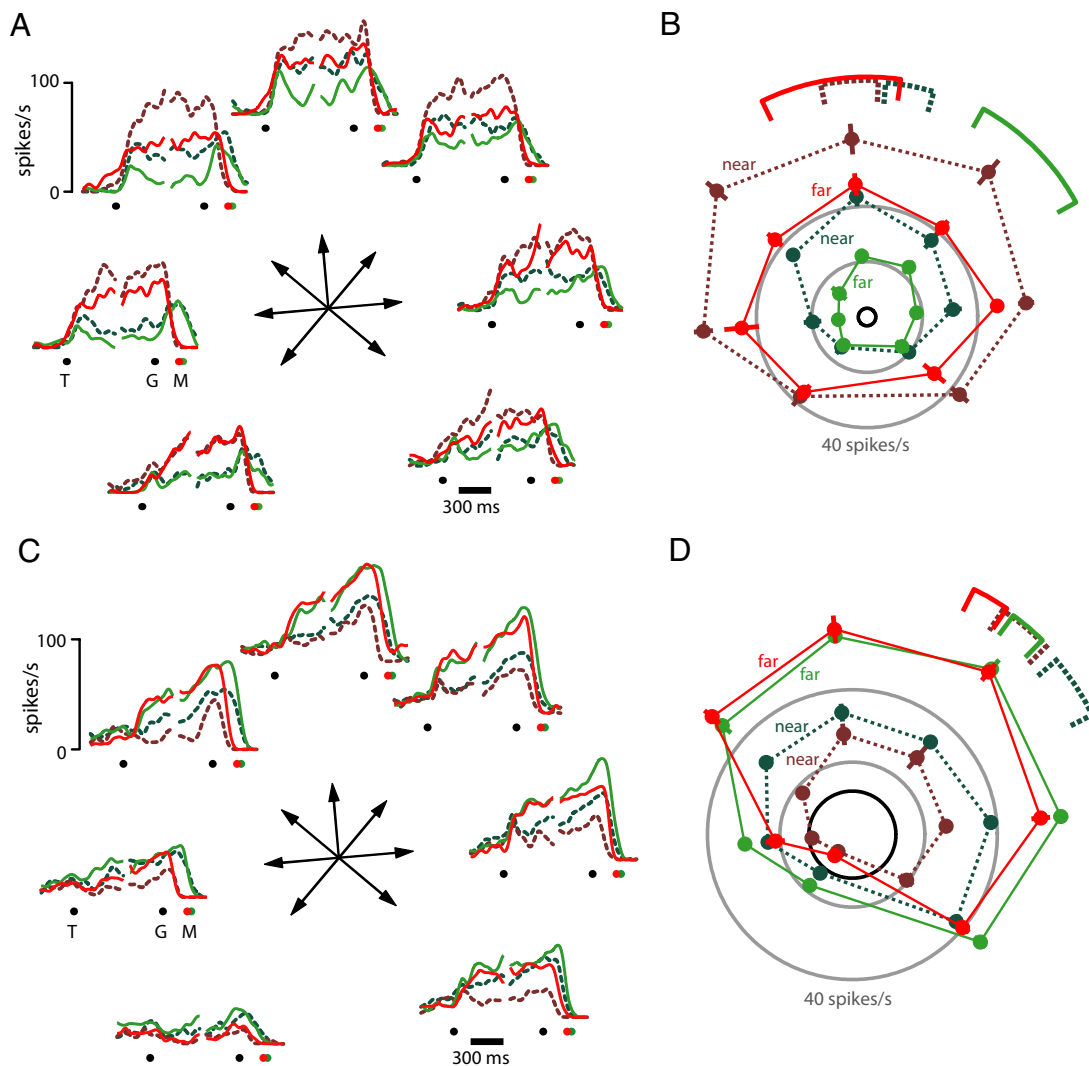


FIG. 4. Responses of 2 example neurons. In each plot, red and green traces correspond to the instructed-fast and -slow conditions, and dashed and solid traces correspond to the 2 distances (7 and 12 cm). A: mean firing rate as a function of time for one example neuron (A35: monkey A, neuron 35, ~9 trials/condition). Each subpanel plots data for 1 target direction and for both distances and instructed speeds. Mean firing rate was computed twice: once with data locked to target onset and once with data locked to the go cue. These 2 means are plotted with a break between them, a necessity given the variable delay period. The dots at the bottom of each sub-panel show the time of target onset (T), the time of go cue (G), and the median time of movement onset (M) computed separately for the 2 instructed speeds. B: polar plot of mean delay-period firing rate vs. target direction (same neuron as in A). Error bars on each symbol plot the SE across trials. Arcs at the outside of the plot show, for each condition, the preferred direction (PD) ± 1 SE. The black circle at center shows baseline firing rate (mean over the 300 ms preceding target onset). The gray circles provide a scale: 20 and 40 spikes/s respectively. C: mean firing rate as a function of time for a second example neuron (A39, ~14 trials/condition). D: polar plot of delay-period firing rate for that neuron.

resampled (with replacement) the original distribution of firing rates. We then recomputed θ_{pref} and repeated the procedure 1,000 times. For the purposes of graphical presentation and by analogy with a linear scale, we define the SE as the arc from $\theta_{\text{pref}} - \text{SE}$ to $\theta_{\text{pref}} + \text{SE}$ containing 68% of the sampling distribution of θ_{pref} . When asking whether two PDs differ significantly from one another, the sampling distributions of θ_{pref} were artificially centered on 0, so that the two conditions now had the same “true” PD. The P value was then the probability that a random draw from each distribution could yield a difference greater than or equal to the actual measured PD difference.

For multi-sample comparisons (e.g., asking whether the PD varies across all 4 distance/speed combinations), we developed a test based on the circular variance of the four PDs, asking whether this is higher than expected given measurement error (much as an ANOVA does for noncircular data). For each condition, c , (i.e., each distance/speed combination) we computed $\theta_{\text{pref}}(c)$ and $r(c)$, the modulation of the cosine fit, as described above. We then define the circular variance, s^2 , of θ_{pref} across conditions, c , as

$$x = \sum_c r(c) \cos(\theta_{\text{pref}}(c)) / \sum_c r(c) \quad (2a)$$

$$y = \sum_c r(c) \sin(\theta_{\text{pref}}(c)) / \sum_c r(c) \quad (2b)$$

$$s^2 = 1 - \sqrt{x^2 + y^2} \quad (2c)$$

s^2 is highest when θ_{pref} differs across conditions. It is higher if the differing values of θ_{pref} correspond to strongly tuned conditions and lower if the differing values of θ_{pref} correspond to weakly tuned conditions. We then define P as the probability that s^2 could be as large as the measured value, assuming all PDs were actually identical. This was computed numerically, by setting each $\theta_{\text{pref}}(c)$ to be the same, and then repeatedly drawing from the sampling distributions for $\theta_{\text{pref}}(c)$ and $r(c)$. Using simulated data, we verified that this method was reasonably robust in the face of departures from Gaussian sampling noise. Drawing simulated firing rates from a Poisson distribution, the rate at which the null hypothesis was mistakenly rejected (at the $P < 0.05$ level) rose only slightly, from 5 to 6.1%. For both this and the preceding analyses, similar results were found using the vector-sum method (e.g., Georgopoulos et al. 1982; Scott and Kalaska 1997) to estimate the PD.

RESULTS

Behavior

Monkeys performed the task well. Even slow reaches to green targets were fairly swift, with durations of 150–300 ms depending on target distance. Fast reaches to red targets were swifter still, with durations of 100–200 ms. Figure 2 shows an analysis of reach velocity for two representative datasets, one for *monkey A* (left) and one for *monkey B* (right). Reach velocity profiles (*A* and *B*) were roughly bell-shaped and scaled naturally with target distance. For a given distance, peak velocities were higher for red targets than for green targets. A similar pattern is seen at the level of single trials (*C* and *D*). For a given distance, peak velocities are higher for red targets, with only minimal overlap of the distributions. Mean reaction times (from the go cue until movement onset, estimated as the time when hand velocity reached 5% of its peak) ranged from 228 to 246 ms depending on the monkey and task. Reach trajectories (Fig. 3, *A* and *B*) exhibited slightly more curvature for fast reaches, although only for some directions. Reach end points (Fig. 3, *C* and *D*) were similar for the two instructed speeds, although there was often slightly more overshoot for fast

reaches. Direct observation (via infra-red camera) revealed that arm posture was very similar during fast and slow reaches with one notable exception: for rightward targets, *monkey B* tended to “press” more of the hand onto the target at the end of the reach in the instructed-fast condition. In summary, reach end point, path, and posture were similar, although not always identical, for the instructed-fast and instructed-slow conditions. In control analyses presented later, we consider the degree to which this may have impacted effects at the neural level. Overall, we note that reach swiftness and accuracy were such that most humans would require training before they could equal the performance of the monkeys.

Basic characteristics of the recorded neurons

We first consider the 95 neurons for which we obtained a full direction series (7 directions \times 2 distances \times 2 speeds) and which satisfied the inclusion criteria. For each neuron and each condition (i.e., target-location/instructed-speed; 28 total conditions) we computed the mean delay-period firing rate (see METHODS). For 79% (21%) of neurons, the strongest effect was an increase (decrease) in the firing rate from the pretarget baseline. Modulations of the mean rate from baseline ranged from +77 to –36 spikes/s. Taking the most effective condition for each neuron, the mean absolute modulation was 21 spikes/s. This range of effects is in keeping with prior reports (e.g., Crammond and Kalaska 2000; Lecas et al. 1986). The mean number of trials/condition was 14.

Figure 4*A* plots firing rate versus time for one example neuron. Red and green traces correspond to red (fast) and green (slow) targets. Dashed and solid traces correspond to near (7 cm) and far (12 cm) targets. Direction, distance, and instructed speed all influenced the delay-period response, with the largest response preceding fast reaches to near $\sim 90^\circ$ targets. Figure 4*B* plots these data in a summary format. Arcs show the preferred direction (PD), ± 1 SE. Figure 4, *C* and *D*, shows data for a second example neuron, for which the delay-period response was greatest for far, $\sim 45^\circ$ targets. Instructed speed had little effect at that distance (solid green and red traces largely overlap). However, for near targets firing rates were consistently higher for *slow* reaches (dashed traces: green $>$ red).

The examples in Fig. 4 illustrate a number of features typical of recorded responses. First, delay-period activity often showed a large influence of instructed speed in addition to the previously known influence of target direction and distance (ANOVA, $P < 0.0001$ for all main effects for both neurons). Second, interactions among the effects of direction, distance, and speed were common. For example, for the neuron shown in the *bottom panels*, speed had an effect primarily for near targets (ANOVA, interaction, $P < 0.001$). Third, despite such interactions the effect of distance cannot, in general, be secondary to that of speed (as might be suggested by the natural increase in reach velocity with distance). The first example neuron (*top panels*) fired most strongly for *near* targets and the *fast* instructed speed, whereas the second (*bottom panels*) fired most strongly for *far* targets and the *slow* instructed speed. Fourth, although direction tuning was typically robust, it was not always invariant. For the first neuron in particular, PDs are similar but not identical across the different distances and instructed speeds. We report in the following text population

analyses that further describe these findings. Figure 5 shows additional examples that illustrate the range of observed effects, which can be difficult to convey using population-level analyses alone.

Population analyses: impact of target direction, distance, and speed

Of 95 tuned neurons, 92% showed a main effect of direction ($7 \times 2 \times 2$ ANOVA, $P < 0.05$). This number was slightly higher (95%) if we included significant interactions involving direction. This prominence of delay-period direction tuning is consistent with many prior studies of PMd and M1 (e.g., Georgopoulos et al. 1989a; Messier and Kalaska 2000; Riehle and Requin 1989; e.g., Tanji and Evarts 1976; Wise and Kurata 1989). Also in agreement with prior work (Messier and

Kalaska 2000; Riehle and Requin 1989), we found that delay-period responses were influenced by target distance: 62% showed a main effect, whereas 78% showed some effect (main or interaction) involving distance. Some neurons responded more briskly for far targets (e.g., B72), others responded more briskly for near targets (e.g., A19), and a few seemed insensitive to distance (e.g., A29). To ask whether there was an overall tendency to prefer near or far targets, we considered each direction/instructed-speed combination separately (a total of $95 \times 7 \times 2$ comparisons). This was done because the preferred distance sometimes varied with direction/instructed-speed. Of comparisons with a significant (t -test, $P < 0.05$) effect of distance, 69% (31%) involved a preference for far (near) targets. Thus there was an overall tendency for the more distant targets to evoke higher firing rates, but the opposite effect was not uncommon.

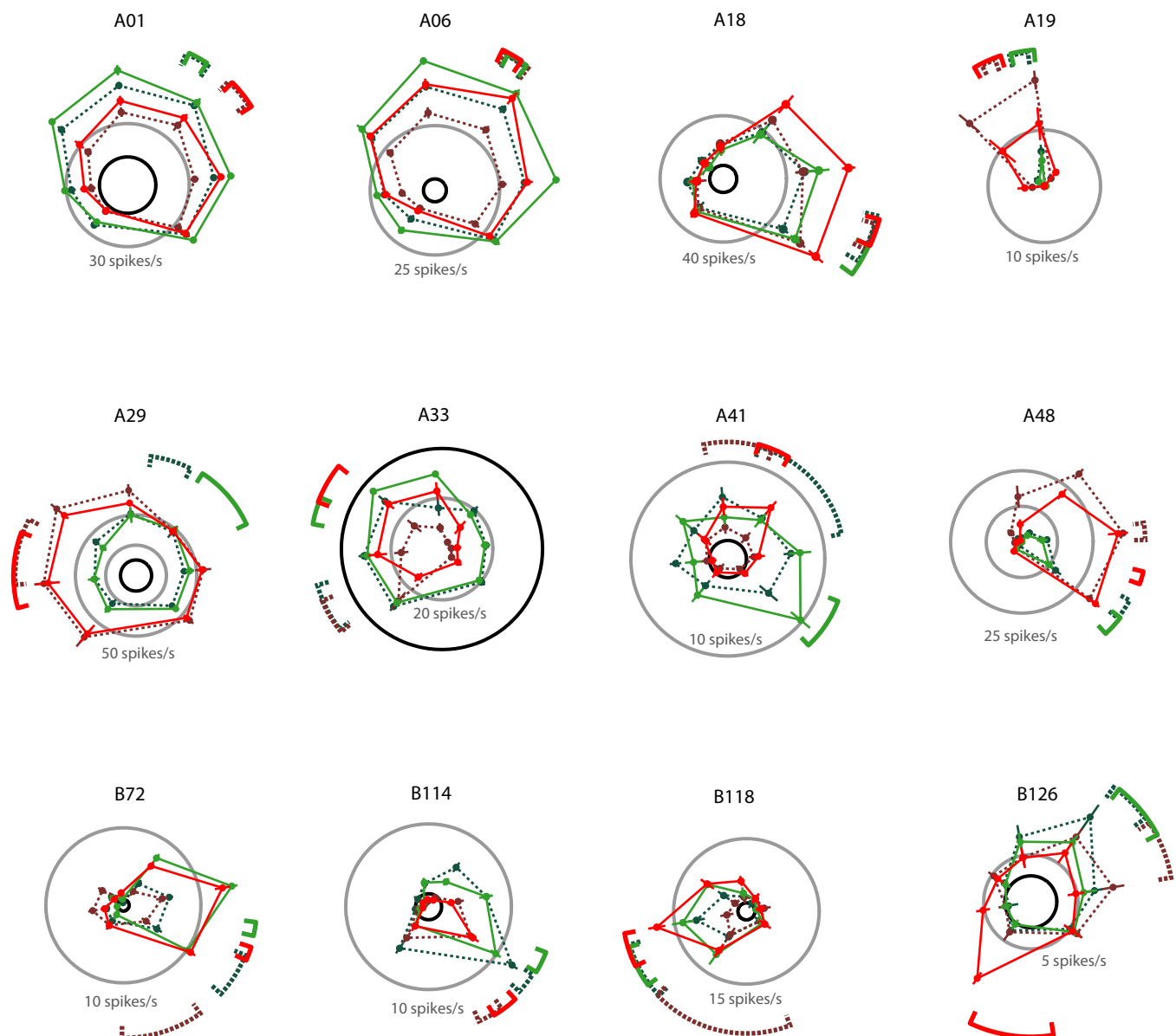


FIG. 5. Responses of 12 example neurons, illustrating the range of observed responses. Each subpanel shows a polar plot of delay-period firing rate versus target direction (same format as for Fig. 4, B and D). Neuron identities are given at the top of each panel. Labels (in spikes/s) indicate the scale provided by the outer gray circle.

Our primary new finding is that the instructed speed has a large influence on delay-period responses. Of tuned neurons, 74% showed a significant main effect of speed, and 94% showed some effect (main or interaction) involving speed. Firing rates could be higher before instructed-fast reaches (e.g., A19, A29) or before instructed-slow reaches (e.g., A01, B114). To determine which preference was more common, we performed an analysis similar to that for distance in the preceding text. Considering each direction/distance combination separately (a total of $95 \times 7 \times 2$ comparisons), 61% (39%) of significant effects involved a preference for fast (slow) reaches. Thus there was an overall tendency for the fast instructed speed to evoke higher firing rates, but the opposite effect was not uncommon. As mentioned in the preceding text, it was also not uncommon for a neuron to prefer far targets and the slower instructed speed (e.g., A01, A06) or to prefer near targets and the faster instructed speed (e.g., A19).

In summary, most neurons showed a statistically significant impact (main effect or interaction) of target direction (95%), distance (78%), and instructed speed (94%). To compare effect magnitudes, for each neuron we measured the maximum modulation caused by each factor (see METHODS). Averaged across all neurons, this modulation strength was 18 spikes/s for direction, 10 spikes/s for distance, and 11 spikes/s for speed (SE = 1 in each case). Table 1 summarizes these findings, and gives values for each monkey separately. Of course, the relative impacts will depend on the range spanned by each parameter. In particular, directions spanned most of the two-dimensional range, whereas peak velocities differed by only about a factor of two between instructed speeds. It is therefore difficult to draw firm conclusions about relative influence. What is clear is that delay-period responses are strongly influenced by all three parameters, and the influence of one can depend on the values of the others.

Changes in preferred direction with distance and instructed speed

For each neuron (95), the PD was computed for each distance and instructed speed (4 conditions). Figure 6A plots the distribution of all (380) such PDs. There was a modest bias toward rightward directions ($P < 0.001$, Rayleigh's test; $P < 0.05$, Rao spacing test). For a given neuron, PDs tended to be similar across conditions, but it was not uncommon for the PD to depend on distance (e.g., Fig. 5, A33), instructed speed (e.g., A29) or an interaction of the two (e.g., B126). A statistical interaction ($7 \times 2 \times 2$ ANOVA, $P < 0.05$) of direction with

distance or speed was observed for 71% of neurons. Not all such interactions indicate a PD change (some reflect changes in response gain or sharpness), but in many cases, the PD did rotate. Focusing first on the effect of distance, for each neuron and each instructed speed, we computed the difference between the PDs for the two target distances. Figure 6B plots the distribution of absolute differences (gray bars). Most differences were small, but differences $>40^\circ$ were not uncommon. Of 190 comparisons, 21% showed a significant ($P < 0.05$) PD change with target distance (black bars). The mean change across all comparisons was 35° . Of course, statistical noise will tend to inflate this measurement. Even for truly identical PDs, there would always be a measured difference due to sampling error. The gray trace gives the expected distribution of such effects, estimated using a bootstrap procedure (see legend). Large measured rotations were considerably more prevalent than expected by chance. PDs could also differ between instructed speeds: 32% of such comparisons showed a significant rotation (Fig. 6C), with a mean change of 39° . Not surprisingly, PDs were most likely to differ when both distance and instructed speed differed (e.g., between a slow/short reach and a fast/long reach). The mean rotation was 45° and was significant for 33% of comparisons (Fig. 6D). Note that if PDs were uncorrelated between conditions, the mean difference would be 90° .

The analyses in the preceding text ask whether the PD rotates between a given pair of conditions. One would like to test the null hypothesis that the PD is the same across *all four* distance/speed combinations. To do so, we measured the circular variance of those four directions (see METHODS), and computed P , the probability that this would be equaled or exceeded due to measurement variability alone. This computation is roughly equivalent to an ANOVA on a circular scale. Of our subset of 95 tuned neurons, 45% showed a significant ($P < 0.05$) impact of condition on the PD. Finally, we examined the prevalence of effects along the rostrocaudal gradient of recording sites. Neither the impact of instructed speed nor the size of preferred-direction rotations varied significantly with cortical location. Of course, the lack of effect may simply be due to the limited range of sites tested (we did not test sites in rostral PMd, and recorded only a modest number of delay-active neurons in the central sulcus) and limited statistical power. In particular, for both monkeys the effect of instructed speed did tend to be somewhat larger for more caudal sites ($P = 0.76$ and $P = 0.056$). We also note that we observed no

TABLE 1. Incidence and magnitude of effects

	<i>n</i>	Significant Effects			Modulation Strength, spikes/s			PD Change	
		Direction	Distance	Speed	Direction	Distance	Speed	Significant	Mean Δ
Direction series (monkey A)	46	96%	70%	93%	23	11	14	39%	40°
Direction series (monkey B)	49	94%	86%	94%	13	8	8	51%	49°
Direction series (total)	95	95%	78%	94%	18	10	11	45%	45°
Distance series (monkey B)	41	85%	83%	98%	10	10	10	-	-

Data are split by task (direction vs. distance series) and monkey. Entries under *n* give the number of neurons analyzed (after selection as described in METHODS). Entries under significant effects give the percentage of significant effect ($P < 0.05$ for main effect or interaction) for target direction, distance, and instructed speed. Modulation strength is as defined in the text (Eq. 1). For preferred direction (PD) changes, entries under significant give the percentage of neurons with a significant effect using the test of circular variance. Entries under mean Δ give the mean change in PD when both target distance and instructed speed were changed.

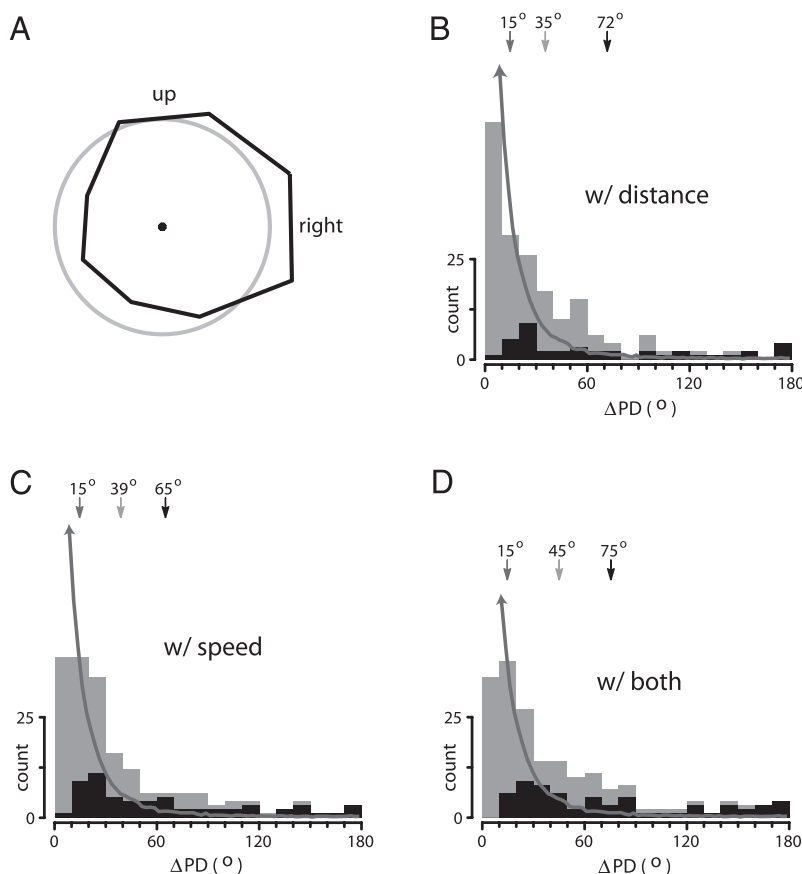


FIG. 6. Distributions of PDs (A), and of PD differences between conditions (B–D). A: distribution (in 45° bins) of all measured PDs. For reference, the gray circle plots a uniform distribution. B: distribution of (absolute) PD differences when target distance changed. For each neuron/instructed speed, we computed the difference between the PDs for the 2 target distances. Gray bars show the distribution for all 190 differences. Individually significant ($P < 0.05$) differences are shown in black. The gray trace shows the distribution of PD differences expected from sampling error, estimated via a bootstrap procedure. For each condition, we computed the PD, re-sampled the data (with replacement), computed a new PD, and took the absolute difference. Repeating this 100 times for each neuron, distance, and instructed speed yielded the distribution shown by the gray trace (scaled to have the same area as the original measured distribution). The trace is truncated at small values where it becomes large. Arrows show the means of the 3 distributions (expected, actual, significant changes only). C: similar analysis but for PD differences between instructed speeds. Each neuron contributes 2 values, 1 per distance. D: similar analysis for PD differences when both distance and instructed speed differed. Each neuron contributes 2 values: 1 when comparing near/slow with far/fast and 1 when comparing near/fast with far/slow.

significant tendency for rotations to be clockwise versus counterclockwise.

Further examination of the impact of target distance

Data from the distance series allow more detailed examination of the impact of target distance and of possible interactions between distance and speed. Targets were presented at five distances (from 3 to 12 cm) in the preferred and anti-preferred directions of the neuron under study, estimated from a preliminary direction series. As the PD can differ across distances/instructed-speeds, there is no guarantee that we selected the ideal axis (indeed, there may be no single ideal axis). Still it is expected that the chosen axis should produce strong modulation in most cases. Of 51 neurons tested, 41 passed the criteria for inclusion in our analysis. The examples in Fig. 7 illustrate some typical effects. All three neurons were tuned for direction, distance, and speed ($2 \times 5 \times 2$ ANOVA, $P < 10^{-6}$ for all main effects). The neuron in A showed sharp tuning for distance and a strong effect of instructed speed. The neuron in B showed a less dramatic but still sizeable impact of distance: increases from 34 to 61 and 55 to 75 spikes/s for the instructed-slow and -fast conditions. The neuron in C preferred the instructed-slow condition for most locations. One might expect such a neuron to prefer reaches to near targets, given their lower peak velocities. Yet delay-period firing rates increased with distance: from 9 to 29 and 20 to 28 spikes/s for the instructed fast and slow conditions. There was also a significant interaction between distance and instructed speed ($P < 0.002$). Figure 8 plots responses, in summary format, for 15

example neurons (including the 3 shown in Fig. 7). Mean delay-period firing rate is plotted versus target distance for both the preferred (*right*) and null (*left*) directions. These examples illustrate a number of general observations that are substantiated by further population analyses. Just as importantly, these examples illustrate the considerable heterogeneity of response patterns, something that can be difficult to capture given population analyses alone.

Of the 41 neurons that passed the criteria for inclusion, 78% showed a main effect of direction ($P < 0.05$) and 85% showed some effect (main or interaction) involving direction. For distance, 66% showed a main effect and 83% showed some effect. For instructed speed, 90% showed a main effect and 98% showed some effect. The modulation strength (see METHODS) was 10 spikes/s for all three factors (SDs ranged from 7 to 8 spikes/s; the SE was 1 spike/s in each case). Thus distance tuning is relatively more prominent than it was for the direction series (now being equivalent in strength to direction tuning). This is unsurprising, as we are now testing five distances (rather than 2), and two directions (rather than 7).

Regarding distance tuning, a response increase with distance was the most common pattern (e.g., B24), whereas declines were less common (e.g., B51, instructed slow). To quantify this, we consider neurons/instructed speeds where there was a significant firing-rate difference between 3 and 12 cm. Of these, a preference for the greater distance was observed in 77 versus 23% of cases. This was true even for the null direction (74 vs. 26%). Clear tuning for an intermediate distance (e.g., B30, instructed-fast condition) was only rarely observed. For

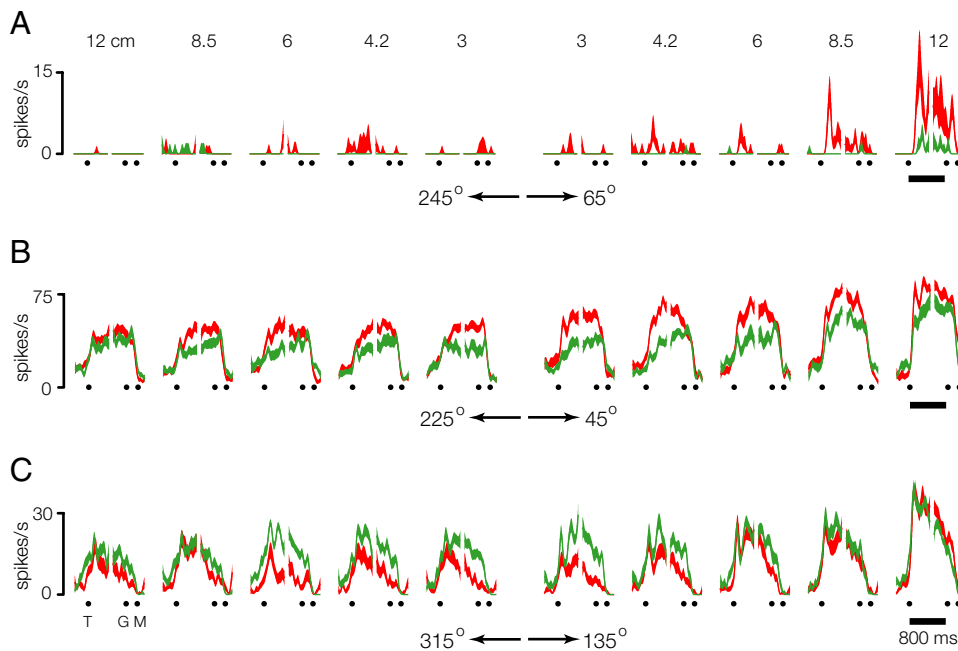


FIG. 7. Responses of 3 example neurons for the distance series. Each subpanel plots mean firing rate as a function of time for both instructed speeds (red and green traces) for a given target location. Targets were presented at 5 distances (3–12 cm) in both the preferred direction (*right*) and the opposite direction (*left*). Mean firing rates were computed twice—once with data locked to target onset, once with data locked to the go cue—and are plotted with a break between these 2 means. Dots at the bottom of each subpanel show the time of target onset (T) the time of the go cue (G), and the median time of movement onset (M). Trace width indicates ± 1 SE. A: responses of neuron B37 (~ 17 trials/condition). B: responses of neuron B24 (~ 23 trials/condition). C: responses of neuron B11 (~ 21 trials/condition).

only 1% of neurons/instructed speeds was the response to an intermediate distance significantly higher (*t*-test, $P < 0.05$) than the responses at the extrema. It is thus difficult to ask how frequently the preferred distance changed with instructed speed. However, we can readily inquire how often the slope was altered. Restricting analysis to the preferred direction, the slope of firing rate versus distance (measured via regression) differed significantly between instructed speeds 54% of the time. Rarely (12% of the time) the slope reversed between the two instructed speeds (e.g., B40), although this was never a statistically significant effect. Such reversals were more common for the anti-preferred direction (e.g., B41), occurring for 39% of neurons. However, such effects were usually small, and were statistically significant for only 5% of cases.

Regarding speed tuning, a preference for instructed-fast reaches was most common. Of target locations where there was a significant response difference (*t*-test, $P < 0.05$) between the two instructed speeds, the fast instruction was preferred in 78 versus 22% of instances. The effect of instructed speed could depend on distance. Overall, 32% of neurons showed either a significant interaction of speed with distance or a significant interaction among all three factors. Such interactions took a variety of forms. For example, it was common for the instructed speed to matter at only some target locations (e.g., B11, B49). Occasionally the impact of the instructed speed could even reverse as target distance changed (e.g., B18, B51), though such effects were significant in only 7% of neurons. In general, the responses of neurons showed a number of features that might be considered unexpected: a preference for slow speeds but far targets, different distance tuning depending on instructed speed, reversals of speed tuning depending on distance, and so forth. Any individual unexpected feature might occur only rarely, yet the result at the population level is a considerable heterogeneity of response patterns, something that can be fully appreciated only by inspecting many examples.

Controls: correlations between behavioral parameters

The preceding analyses employ three experimentally controlled variables: target direction, distance, and instructed speed. Modulations of delay-period activity were observed with respect to each of these variables. However, it should be stressed that these variables correlate with each other and with a wide variety of other factors, some measured, some not. This issue will be taken up again in the discussion when considering the evidence for “fundamental” tuning dimensions. At present, a critical issue is whether some of the correlations between behavioral parameters might render our findings trivial. We consider a number of possibilities.

If neurons exhibit distance tuning and the actual reach distances differ slightly between instructed speeds, then might that explain the impact of speed? This is very unlikely. Although instructed-fast reaches tended to have more overshoot, this was a small effect and was present for only some reach directions. Even for those directions, endpoint differences clearly can’t explain effects for those neurons that prefer slow *and* far or fast *and* near. Finally, we have re-plotted the data from the distance series (as in Fig. 8) against the *actual* mean reach distance for each condition. The effects of instructed speed are still very much present. Might the converse be true? Might distance tuning be secondary to speed tuning? This is unlikely because, as discussed in the preceding text, speed and distance tuning could “disagree.” We have also re-plotted the data from the distance series (as in Fig. 8) with the average peak reach velocity on the *x* axis. If the influence of distance were simply due to tuning for peak velocity, then this exercise ought to bring the data for the two instructed speeds into register. In fact, this happened very rarely. Thus, although it would be rash to conclude that distance and speed are orthogonal tuning dimensions, one is not a trivial consequence of the other.

For some reach directions there were small differences in initial reach direction between the instructed speeds. Given that neurons are strongly directional, might this create an artifactual

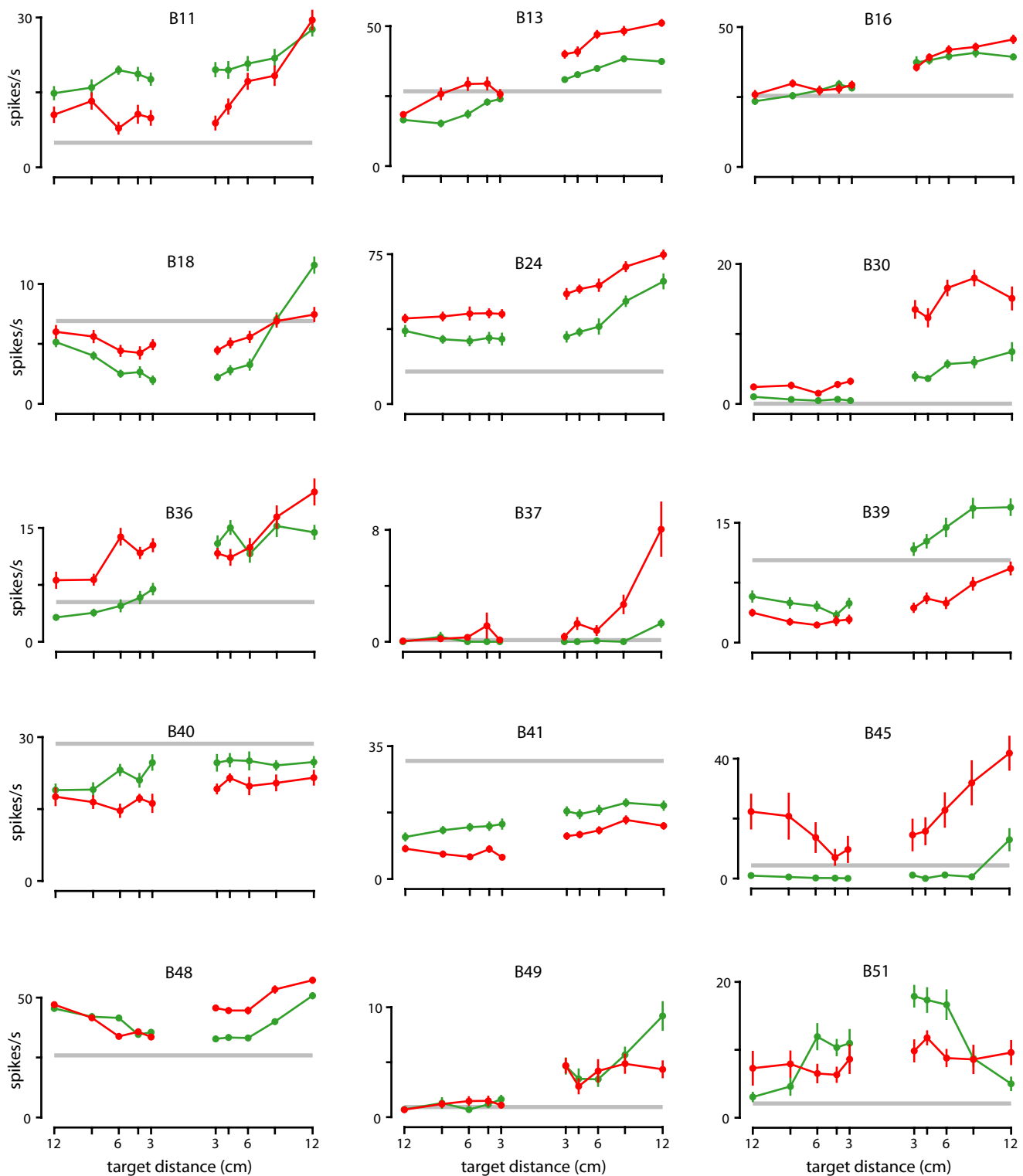


FIG. 8. Responses of 15 example neurons for the “distance series.” Each subpanel plots the mean delay-period response vs. target distance (3–12 cm) and direction (preferred to the right, opposite to the left). Data for the instructed-fast and -slow conditions are shown in red and green, respectively. Bars show the SE. Horizontal gray lines show the mean baseline firing rate.

tuning for instructed-speed? This is unlikely, as direction tuning was typically broad and differences in initial reach direction were modest. Furthermore, such differences were not present for all directions. For example, the reaches of *monkey B* to targets in the 0–90° range had very similar paths for the

two instructed speeds (Fig. 3*B*). Yet it was common for neurons recorded from that monkey to show large effects of instructed speed for such targets. If small differences in initial reach direction don’t create the basic effect of instructed speed, then might they create the PD rotations? In principal they

could, if direction tuning relates to the initial reach direction but we express it relative to target direction. However, differences in initial reach direction (measured from 100 ms before movement onset to 75 ms after) between distances/instructed speeds were modest (mean differences were 7 and 9°, respectively). They are thus unlikely, a priori, to account for the observed PD differences (which could be >90°). Furthermore, using the circular variance method (see preceding text), PDs were just as likely to rotate when based on the initial reach direction (47% with significant effects) as when based on target direction (45%).

Possible contributions of oculomotor behavior

It has been previously reported that delay-period responses in PMd can be influenced by gaze location (Batista et al. 2004, 2005; Boussaoud 1995; Boussaoud et al. 1998; Cisek and Kalaska 2002a; Nelson et al. 2005). Might some or all of the observed influence of direction, distance, and instructed speed be indirectly due to eye position effects? *Monkey A* typically fixated the central spot throughout the delay, and made a saccade to the target only after the go cue (Fig. 9A). Thus gaze location during the delay was similar for all target locations and cannot account for the observed tuning. *Monkey B* exhibited the opposite behavior, typically fixating the target early in the delay (Fig. 9B). For this monkey, it is possible that direction and distance tuning during the latter part of the delay were influenced by eye position. However, eye position was typically similar for red and green targets and thus cannot account for the observed effects of instructed speed.

In general, there were no obvious neural consequences of the different oculomotor strategies of the two monkeys. For example, it certainly wasn't the case that tuning emerged only after the saccade for *monkey B*. That said, one certainly suspects that saccade-locked analyses might reveal effects, an issue we leave to future studies. For the moment, the critical observation is

that the effects of instructed speed cannot be secondary to oculomotor behavior because 1) similar effects were observed in two monkeys with opposite fixation strategies, 2) for neither monkey did fixation strategies differ between the two instructed-speeds, and 3) the effects of instructed-speed emerged (even for *monkey B*) before saccades were made.

Temporal evolution of effects

Prior studies have addressed the possibility that there is a temporal ordering to the representation of movement parameters during motor preparation (Messier and Kalaska 2000; Riehle and Requin 1989; Riehle et al. 1994). Our experiments were not designed to address these issues, but some information can nevertheless be gleaned. We first asked how quickly the effect of direction, distance and speed developed. For instructed speed, we took the difference between responses to the preferred and nonpreferred speeds as a function of time. For each neuron, this was done for the direction/distance combination where the effect of instructed speed (computed across the whole delay) was maximal. Absolute response differences were then averaged across neurons. The same was done for the effect of direction (measured at its best distance/speed) and distance (measured at its best direction/speed). Results are plotted in Fig. 10. The impact of direction on firing rate (black trace) evolves somewhat more rapidly than that for distance (light gray) or instructed-speed (dark gray). However, this difference was more pronounced for the direction series (A) than the distance series (B), somewhat complicating interpretation. That said, the more rapid evolution of directional information in A is not simply due to the larger magnitude of the direction effect. The rapid time course was preserved for the firing-rate difference between nonpreferred directions 90° apart (dashed trace in A). C shows a related analysis of the time course for PD difference between conditions. PD differences

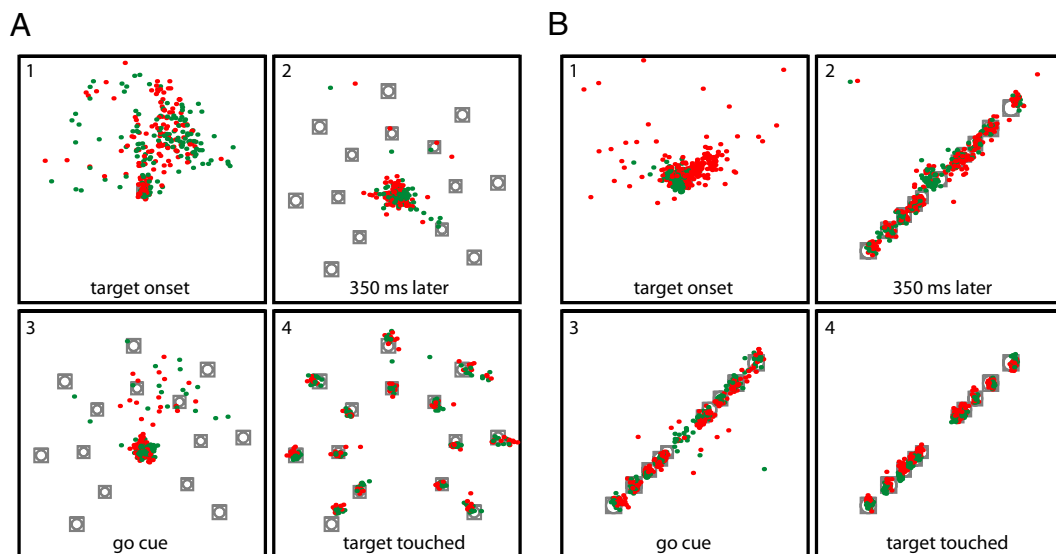


FIG. 9. Gaze location during the course of the trial. A: data for *monkey A* (same dataset as in Figs. 2, A and C, 3, A and C, and 4, A and B). The 4 subpanels plot the horizontal and vertical location of fixation at the time of target onset (1), 350 ms later (2), the time of the go cue (3), and the moment the target was touched (4). Data are shown for every recorded trial, with red/green dots corresponding to instructed-fast/instructed-slow trials. Squares (circles) correspond to the red (green) targets. This monkey typically fixated the central touch-point (and/or his own hand) for the duration of the delay and made a saccade to the target only after the go cue. B: similar plot but for *monkey B* from the same dataset as the example neuron in Fig. 7B. This monkey typically made a saccade to the target during the delay.

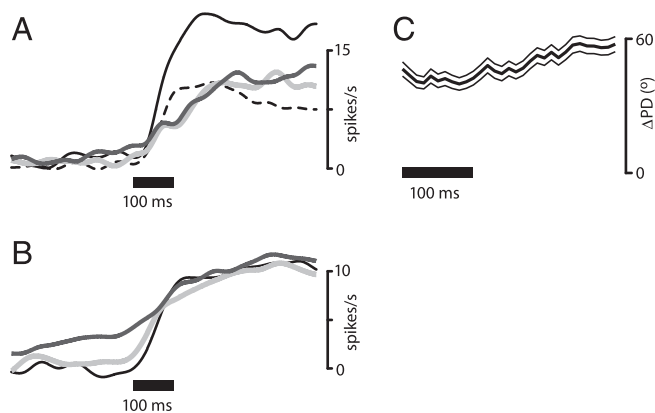


FIG. 10. Time course of different effects. **A**: temporal evolution of the influence of direction (black trace), distance (light gray trace) and instructed speed (dark gray trace) on delay-period firing rates. Each trace plots the influence (computed as described in the text) of that parameter as a function of time, relative to target onset (occurring at the left side of scale bar). The dashed trace plots the influence of direction but computed between nonpreferred directions that were 90° apart, rather than between the preferred and null directions. Data are averaged across all neurons for both monkeys. To ensure minimal distortion of the time courses, this analysis used a slightly shorter (20 ms rather than 25 ms SD) Gaussian filter. Data are for the direction series. **B**: same as in **A** but for the distance series. **C**: effect of instructed speed and distance on the PD as a function of time. The PD was computed using a sliding 100-ms window. For each window position, and for each neuron, we computed the absolute change in PD when both distance and instructed speed differed (2 values/neuron, same computation as for Fig. 6D). The mean (\pm SE) is plotted as a function of the starting position of the window. The trace begins with a window starting 50 ms after target onset.

became slightly stronger with time but were certainly common early in the delay period.

Unlike prior studies (e.g., Riehle and Requin 1989, 1993; Riehle et al. 1994), we did not endeavor to deliver partial prior information in a systematic way. However, some partial prior information was available: the instructed speed (unlike the direction and distance) was known before target onset. The central spot, the appearance of which initiated the trial, received the same color coding as the target, a feature intended to aid training. To some degree, monkeys must have attended to this information as differences in firing rate between the two instructed speeds were occasionally observed before target onset. This effect was much more prominent for the distance series (Fig. 10B) than for the direction series (A). This is unlikely to be a training effect, as data for the distance series were collected first.

Decoding a complex neural code

When neural responses are influenced by a given parameter (e.g., reach direction), it is often said that those responses *code for* or *represent* that parameter. The implication is that other areas extract information about that parameter. As will be stressed in the DISCUSSION, we believe it is unclear whether this is a productive way to think of activity in PMd/M1. Nevertheless, it is worth asking whether a hypothetical extraction would be impaired by the interactions and inconstancies observed in our data. Formally, it is almost trivially true that extraction needn't be impaired, as the dimensionality of the neural response is typically higher than the dimensionality of the information we are trying to extract. Consider our population of 95 units recorded using the direction series. If one wishes to

extract target locations for the 28 conditions used, then this can be accomplished with zero error. Starting with a 28×95 dimension matrix of delay-period responses, R , we wish to reconstruct a 28-dimension vector, \mathbf{t} , of target locations (or any other parameter). There will typically be infinitely many choices of a 95 dimension weight vector, \mathbf{w} , such that $R * \mathbf{w} = \mathbf{t}$. Thus a lack of invariant tuning needn't hamper accurate extraction of information, so long as neural responses vary with the parameter to be decoded, different neurons vary with that parameter in different ways, and we are given our choice of weights.

What if we do not allow arbitrary weights, but extract the values of the weights directly from each neuron's tuning? To examine this, we employed the well-known population vector (Georgopoulos et al. 1989b; Moran and Schwartz 1999a). Each neuron was assigned a preferred direction vector, \mathbf{d}_n , of unit length (to yield a single PD this was based on the mean response for each direction across distances/speeds). The population vector for a given condition was then $\mathbf{p} = \sum(\mathbf{d}_n * r_n)$, where r_n is the response of neuron n for that condition (computed after subtracting the mean response across conditions, and normalizing by the modulation of the cosine fit). As is shown in Fig. 11, the population vector always pointed roughly in the direction of the target/reach. For a given instructed speed, the population vector was almost always longer for the greater distance. For a given distance, the population vector was usually longer for fast reaches than for slow. Thus the simple population vector provides a reasonable but imperfect readout. Such imperfections were typically more prevalent if the population vector was based on subsets of our population (e.g., the units from only 1 monkey, data not shown). This suggests that for a very large population, the imperfections might average out completely. Of course, whether this would actually be the case is impossible to say from our data.

Muscle preferred directions

The hope that the lack of PD invariance could average out at the population level assumes the existence of a downstream

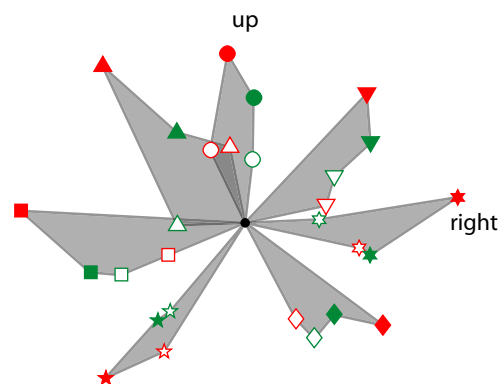


FIG. 11. Population vector computed for the 28 target conditions. The scale is arbitrary. Symbols show the end point of each population vector relative to the origin (black dot). Vectors for the instructed-slow (instructed-fast) conditions are shown in green (red). Vectors for near (far) targets are shown by open (filled) symbols. Vectors for the different target directions are plotted using different symbols and grouped by the shaded polygons. To allow fair combination of the data for the two monkeys (collected using directions rotated 5° with respect to each other), data for both were rotated so that the direction nearest upward (95° or 100°) was considered to have been exactly 90° .

representation of direction that *actually is invariant*. Yet it does not appear that the PDs of *movement-related* activity in PMd/M1 are invariant when tested using this task (Churchland and Shenoy 2005). The same can be said of EMG activity, as is shown by the example recording in Fig. 12A. This muscle (the latissimus dorsi) was responsive during the latter part of the reach. However, the PD differed by 70° between the instructed-fast and -slow conditions. PD rotations were common across the 16 EMG recordings made using the direction series. Figure 12B plots the distribution of PD rotations when both instructed speed and reach distance changed (same format as Fig. 6D). The mean (absolute) change was 65°, slightly larger than for delay-period neural activity (45°). Furthermore, for some muscles the EMG activity was multi-phasic (see Churchland et al. 2006; supplemental data), so that the PD

changed with time. It is unclear whether the neural PD rotations are in any way related to these muscle PD rotations. Still, the prevalence of the latter suggests that there is nothing intrinsically “problematic” about PD rotations at the neural level.

As an aside, tonic EMG activity during the delay was common, as expected given the outstretched position of the arm. As illustrated by the recording in Fig. 12A, this tonic activity was typically un-tuned (open symbols, red and green almost entirely overlapping). An exception was the trapezius of *monkey B*, which showed a small increase in delay-period activity for slow rightward targets. Still, even those changes were small compared with the changes during the reach (Churchland et al. 2006; supplemental data¹). Thus with that minor exception (and with the caveat that we did not record from all muscles), changes in neural activity during the delay period are most naturally interpreted as being related to preparatory processing rather than to the immediate production of muscle contraction.

DISCUSSION

Influence of instructed speed on delay-period activity

Our principal novel finding is that delay-period preparatory activity is influenced by the speed of an instructed movement. For the direction-series task, the impact of instructed speed was intermediate between that of direction and distance, both in terms of neurons showing a significant effect (94 vs. 95 and 78%), and the magnitude of modulation (11 vs. 18 and 10 spikes/s). A more fair comparison is perhaps provided by the distance series, which employed the same number (2) of directions and instructed speeds. For this task, neurons were at least as likely to show a significant effect of speed as of direction (98 vs. 85%) with comparable firing rate modulations (10 spikes/s for each). Prior work has stressed the visuospatial (Buneo et al. 2005; Nelson et al. 2005; Shen and Alexander 1997b) or at least spatial (Shen and Alexander 1997a) nature of delay-period activity in PMd and M1, although experiments have also demonstrated that such activity reflects factors other than reach endpoint/target location (Godschalk et al. 1985; Gomez et al. 2000; Hocherman and Wise 1991; Riehle et al. 1994). In this context, the current results demonstrate that delay-period activity robustly reflects *nonspatial* aspects of how the reach is to be executed. (By nonspatial we mean influenced by something other than the spatial location of the target/reach-trajectory. The influence of instructed speed could of course be due to different activation patterns of the muscles, which are certainly distributed in space.) We also note that a prior study found that *target* speed influenced delay-period activity (Johnson et al. 1999). Our results suggest that the influence of target speed in that study may have been related in part (but probably only in part) to the different reach speeds necessary to strike targets moving at different speeds.

Although theoretical and behavioral studies have often assumed that motor planning is primarily spatial (e.g., van Beers et al. 2004), the finding that nonspatial features are also represented in preparatory activity is not surprising. If preparatory activity is part of a causal chain that will eventually generate movement, then presumably all aspects of the move-

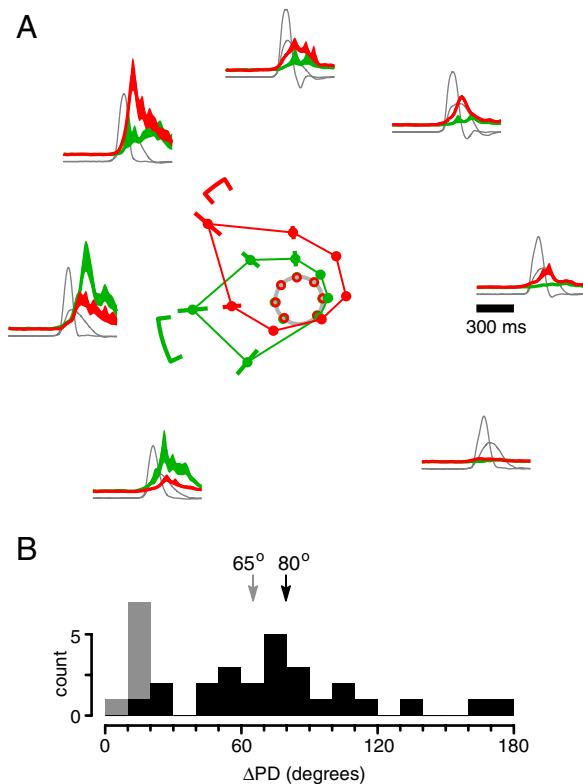


FIG. 12. PDs for EMG. A: EMG activity recorded from the latissimus dorsi of *monkey A* during reaches to the 12-cm distant target at both instructed speeds (red and green traces/symbols). Each subpanel at the outside plots, for a given target direction, the mean EMG signal (\pm SE) as a function of time, overlaid on mean hand velocity traces (gray). All means were computed with respect to movement onset. The polar plots at center show the directional tuning of the EMG for 2 epochs. Open symbols plot the average EMG preceding movement onset (averaged from the start of the trace, 420 ms before movement onset, until 150 ms before movement onset). Filled symbols plot the movement-related EMG, averaged over a 400-ms window beginning 100 ms before movement onset. Bars show standard errors. Arcs at the outside plot the PD of the movement-related activity, \pm 1 SE. The gray circle plots an arbitrary scale. B: distribution of the absolute PD differences when both distance and instructed speed were changed (same format as for neural data in Fig. 6D). Black bars plot statistically significant differences. Arrows give the mean for all differences (gray) and for the statistically significant differences (black). PDs were based on movement-related EMG averaged over the period described in A. A total of 30 comparisons were made for 15 EMG recordings (slow/near vs. fast/far yielded 1 comparison, slow/far vs. fast/near another). Data from 1 EMG recording were not analyzed because there was essentially no response during instructed-slow reaches.

¹ The online version of this article contains supplemental material.

ment must be reflected (at least implicitly) in that activity. We note that this is true even for the model of Todorov and Jordan (2002), despite the fact that explicit motor planning is in terms of higher-level goals. For that model, the parameters of the feedback controller must be set before each movement and will reflect a variety of high- and low-level factors. None of this argues that all aspects of the planned movement must be reflected in the delay-period activity in PMd and M1 in particular, but given their direct spinal projections, such an expectation is quite natural.

When is tuning a representation?

PDs were frequently inconstant across target distances/instructed speeds, with significant differences observed for 45% of tuned neurons. These PD rotations might average out across neurons, allowing the population to faithfully represent direction in the abstract. On the other hand, PD rotations may indicate that reach/target direction is not a fundamental tuning dimension. Certainly a number of other variables, including the upcoming muscle activation, co-vary with target direction. Thus, although direction tuning is a prominent feature of delay period responses, it is not clear what is really being represented. Similar points can be made with regards to speed and distance tuning. Tuning for speed might just as likely be related to initial acceleration, final deceleration, reach duration, the desired pattern of muscle activity, or a host of other factors that correlate with reach velocity. It may also be related to a number of “high-level” parameters such as accuracy, effort, or the time in which the monkey believes the movement must be completed. Similar points have been made with regard to tuning for distance (Messier and Kalaska 2000). In general, it is difficult to know when experimentally observed tuning for a particular parameter actually forms the basis of a *representation* for that parameter.

In this context, it is worth considering whether motor preparation necessarily requires the representation of movement parameters in *any* reference frame, spatial or otherwise. In general, useful computations can be performed by neurons with unclear reference frames (Deneve et al. 2001; Pouget et al. 2002; Zipser and Andersen 1988). For the sake of argument, suppose that at the time the movement is triggered, each neuron’s delay-period preparatory activity is translated, directly or indirectly, into a temporal pattern of muscle activity. In the simplest case, the activity of a given muscle would be a weighted sum of these individual temporal patterns

$$M(t) = \sum_i P_i(t_o) m_i(t - t_o) \quad (3)$$

Where $M(t)$ is the muscle activity at time t , $P_i(t_o)$ is the preparatory activity of the i th neuron at the time the movement is triggered, and m_i is the pattern of muscle activity driven by that neuron following the trigger. Presuming nonlinear interactions between neurons, the same idea can be expressed as

$$M(t) = F(P(t_o), t - t_o) \quad (4)$$

We have recently proposed that the purpose of motor preparation is to find a vector of activities \mathbf{P} , such that the desired movement is generated when the trigger is applied. Different movements would require different choices of \mathbf{P} . As a simple consequence, neurons would be found to be tuned for any

movement parameter examined. This “optimal subspace” proposal (Churchland et al. 2006) indicates an important null hypothesis: that contributions of individual neurons could be essentially arbitrary. “Tuning” could still be observed in the absence of *any* fundamental reference frame. One presumes that the relationship between preparatory activity and movement is *not* in fact arbitrary, and that the values of m (or the nature of F) are chosen by the nervous system to optimize something – perhaps the ability to easily find the appropriate \mathbf{P} . This *may* be best accomplished by employing an explicit representation of the movement dimensions that are most relevant to the goals of the animal, yet this needn’t be the case. The chosen mapping from preparatory activity to behavior might not conform to any simple representational framework. This would be consistent with our experimental observations, which revealed considerable heterogeneity in tuning across neurons, and failed to reveal a simple set of parameters that yielded invariant tuning. Of course, we may simply not be plotting our data against the right movement parameters. Perhaps there is a straightforward relationship between PMd preparatory activity and pending muscle activity (certainly both show PD rotations). Still, it is important to at least consider the possibility that no fundamental reference frame exists.

A number of prior results also suggest the absence of a fundamental reference frame. The principal finding of Shen and Alexander (1997b) was that delay-period direction tuning in PMd was more closely tied to the visual location of the target than to the direction of the actual impending reach. Yet both clearly had an effect, in terms of tuning and gain. This argues that the operative reference frame is *neither* extrinsic nor intrinsic. The findings of Scott and colleagues (Scott and Kalaska 1997; Scott et al. 1997) and of Kakei et al. (1999) make a similar point regarding movement-related activity. The PDs of M1 and PMd neurons rotated with arm posture but not in ways adequately captured by either intrinsic or extrinsic reference frames. Such findings may indicate that the activity in question forms a transition between more sensible reference frames (Kakei et al. 2003). Alternately, no clear reference frame may be used. A recent study of the influence of hand and eye position in PMd (Batista et al. 2004, 2005) found that most neurons had tuning that was not retino-centric, limb-centric, or allo-centric. The observation of response properties with no clear reference frame is beginning to seem almost the norm (e.g., Mullette-Gillman et al. 2005) rather than the exception (for review, see Pouget et al. 2002). From a computational standpoint, such properties are not necessarily problematic, and may even confer advantages (Deneve et al. 2001; Pouget et al. 2002; Zipser and Andersen 1988).

Time course and temporal ordering during motor preparation

The impact of reach speed and distance developed more slowly than did the impact of reach direction. Furthermore, information about reach speed had only a weak impact before reach direction and distance became known. A natural interpretation is that some movement parameters (e.g., speed) cannot be “specified” until others (e.g., direction) are fixed (Riehle and Requin 1989). However, in the distance series, instructed speed *did* have a clear impact before target onset.

Perhaps movement speed can be partially specified when the range of possible directions is restricted (in this case to 2). This suggestion is consistent with the finding of Cisek and Kalaska (2002b) that delay period activity can “represent” two targets simultaneously.

The preceding explanations would seem to necessitate that there exist discrete movement parameters (speed, direction) that define the motor plan—else how can there be an obligatory specification order? Yet a similar explanation remains plausible under the optimal subspace hypothesis (Churchland et al. 2006), which does not insist on a sensible reference frame. In this conception, the trajectory taken during motor preparation will typically be curved, something that would likely be preserved if the high-dimensional state space (with each neuron as an axis) were analyzed by collapsing into a lower dimensional space (with experimenter-selected movement parameters on each axis). It would thus seem (and in some sense be true) that certain movement parameters are specified first. Yet this needn't imply that the axes of the lower dimensional space are truly fundamental.

Motor programming and other possible roles of preparatory activity

The preceding discussion assumes that delay-period activity is related to movement preparation/programming, a possibility heavily stressed in prior work (Crammond and Kalaska 2000; Riehle et al. 1994; Wise 1985). Consistent with this interpretation, delay-period activity has typically been observed even when there is little or no change in muscle EMG during the delay (Messier and Kalaska 2000; Tanji and Evarts 1976; Weinrich and Wise 1982), something that was also true in our data. Furthermore, many delay-active neurons actually *stop* responding around the time that movement begins, seeming to prefer preparation to actual movement (e.g., the examples in Figs. 4 and 7). These observations argue that delay-period responses are indeed preparatory in nature. However, such preparation might well involve events other than motor programming. For example, they might modulate spinal reflex gains or bring spinal neurons close to threshold (Tanji and Evarts 1976; Weinrich and Wise 1982). Such influences are readily incorporated into the conception provided by Eq. 4.

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REFERENCES

Bastian A, Schoner G, and Riehle A. Preshaping and continuous evolution of motor cortical representations during movement preparation. *Eur J Neurosci* 18: 2047–2058, 2003.

- Batista A, Yu B, Santhanam G, Ryu SI, and Shenoy KV.** Coordinate frames for reaching in macaque dorsal premotor cortex (PMd). *Soc Neurosci Abstr* 191.197, 2004.
- Batista AP, Santhanam G, Yu BM, Ryu SI, Afshar A, and Shenoy KV.** Heterogeneous coordinate frames for reaching in macaque PMd. *Soc Neurosci Abstr* 363.312, 2005.
- Boussaoud D.** Primate premotor cortex: modulation of preparatory neuronal activity by gaze angle. *J Neurophysiol* 73: 886–890, 1995.
- Boussaoud D, Joffrais C, and Bremmer F.** Eye position effects on the neuronal activity of dorsal premotor cortex in the macaque monkey. *J Neurophysiol* 80: 1132–1150, 1998.
- Buneo CA, Batista A, Jarvis MR, and Andersen RA.** Time-invariant spatial representations in the posterior parietal cortex. *Soc Neurosci Abstr* 288.286, 2005.
- Churchland MM and Shenoy KV.** Movement speed alters distance tuning of plan activity in monkey pre-motor cortex. *Soc Neurosci Abstr* 2003.
- Churchland MM and Shenoy KV.** Complex patterns of motor cortex activity during reaches at different speeds. *Soc Neurosci Abstr* 318.2, 363.8, 2005.
- Churchland MM, Yu BM, Ryu SI, Santhanam G, and Shenoy KV.** Neural variability in premotor cortex provides a signature of motor preparation. *J Neurosci* 26: 3697–3712, 2006.
- Cisek P and Kalaska JF.** Modest gaze-related discharge modulation in monkey dorsal premotor cortex during a reaching task performed with free fixation. *J Neurophysiol* 88: 1064–1072, 2002a.
- Cisek P and Kalaska JF.** Simultaneous encoding of multiple potential reach directions in dorsal premotor cortex. *J Neurophysiol* 87: 1149–1154, 2002b.
- Crammond DJ and Kalaska JF.** Prior information in motor and premotor cortex: activity during the delay period and effect on pre-movement activity. *J Neurophysiol* 84: 986–1005, 2000.
- Day BL, Rothwell JC, Thompson PD, Maertens de Noordhout A, Nakashima K, Shannon K, and Marsden CD.** Delay in the execution of voluntary movement by electrical or magnetic brain stimulation in intact man. Evidence for the storage of motor programs in the brain. *Brain* 112: 649–663, 1989.
- Deneve S, Latham PE, and Pouget A.** Efficient computation and cue integration with noisy population codes. *Nat Neurosci* 4: 826–831, 2001.
- Dum RP and Strick PL.** Frontal lobe inputs to the digit representations of the motor areas on the lateral surface of the hemisphere. *J Neurosci* 25: 1375–1386, 2005.
- Fujii N, Mushiake H, and Tanji J.** Rostrocaudal distinction of the dorsal premotor area based on oculomotor involvement. *J Neurophysiol* 83: 1764–1769, 2000.
- Georgopoulos AP, Crutcher MD, and Schwartz AB.** Cognitive spatial-motor processes. III. Motor cortical prediction of movement direction during an instructed delay period. *Exp Brain Res* 75: 183–194, 1989a.
- Georgopoulos AP, Kalaska JF, Caminiti R, and Massey JT.** On the relations between the direction of two-dimensional arm movements and cell discharge in primate motor cortex. *J Neurosci* 2: 1527–1537, 1982.
- Georgopoulos AP, Lurito JT, Petrides M, Schwartz AB, and Massey JT.** Mental rotation of the neuronal population vector. *Science* 243: 234–236, 1989b.
- Ghez C, Favilla M, Ghilardi MF, Gordon J, Bermejo R, and Pullman S.** Discrete and continuous planning of hand movements and isometric force trajectories. *Exp Brain Res* 115: 217–233, 1997.
- Godschalk M, Lemon RN, Kuypers HG, and van der Steen J.** The involvement of monkey premotor cortex neurons in preparation of visually cued arm movements. *Behav Brain Res* 18: 143–157, 1985.
- Gomez JE, Fu Q, Flament D, and Ebner TJ.** Representation of accuracy in the dorsal premotor cortex. *Eur J Neurosci* 12: 3748–3760, 2000.
- Hocherman S and Wise SP.** Effects of hand movement path on motor cortical activity in awake, behaving rhesus monkeys. *Exp Brain Res* 83: 285–302, 1991.
- Johnson MT, Coltz JD, Hagen MC, and Ebner TJ.** Visuomotor processing as reflected in the directional discharge of premotor and primary motor cortex neurons. *J Neurophysiol* 81: 875–894, 1999.
- Takei S, Hoffman DS, and Strick PL.** Muscle and movement representations in the primary motor cortex. *Science* 285: 2136–2139, 1999.
- Takei S, Hoffman DS, and Strick PL.** Sensorimotor transformations in cortical motor areas. *Neurosci Res* 46: 1–10, 2003.
- Keele SW.** Movement control in skilled motor performance. *Psychol Bull* 70: 387–403, 1968.
- Kurata K.** Distribution of neurons with set- and movement-related activity before hand and foot movements in the premotor cortex of rhesus monkeys. *Exp Brain Res* 77: 245–256, 1989.

- Kurata K.** Premotor cortex of monkeys: set- and movement-related activity reflecting amplitude and direction of wrist movements. *J Neurophysiol* 69: 187–200, 1993.
- Kutas M and Donchin E.** Studies of squeezing: handedness, responding hand, response force, and asymmetry of readiness potential. *Science* 186: 545–548, 1974.
- Lecas JC, Requin J, Anger C, and Vitton N.** Changes in neuronal activity of the monkey precentral cortex during preparation for movement. *J Neurophysiol* 56: 1680–1702, 1986.
- Messier J and Kalaska JF.** Covariation of primate dorsal premotor cell activity with direction and amplitude during a memorized-delay reaching task. *J Neurophysiol* 84: 152–165, 2000.
- Moran DW and Schwartz AB.** Motor cortical activity during drawing movements: population representation during spiral tracing. *J Neurophysiol* 82: 2693–2704, 1999a.
- Moran DW and Schwartz AB.** Motor cortical representation of speed and direction during reaching. *J Neurophysiol* 82: 2676–2692, 1999b.
- Mullette-Gillman OA, Cohen YE, and Groh JM.** Eye-centered, head-centered, and complex coding of visual and auditory targets in the intraparietal sulcus. *J Neurophysiol* 94: 2331–2352, 2005.
- Musallam S, Corneil BD, Greger B, Scherberger H, and Andersen RA.** Cognitive control signals for neural prosthetics. *Science* 305: 258–262, 2004.
- Nelson MJ, Pesaran B, and Andersen RA.** Dorsal premotor neurons encode the relative position of the hand and the eye. *Soc Neurosci Abstr* 363.314, 2005.
- Pouget A, Deneve S, and Duhamel JR.** A computational perspective on the neural basis of multisensory spatial representations. *Nat Rev Neurosci* 3: 741–747, 2002.
- Riehle A, Grun S, Diesmann M, and Aertsen A.** Spike synchronization and rate modulation differentially involved in motor cortical function. *Science* 278: 1950–1953, 1997.
- Riehle A, MacKay WA, and Requin J.** Are extent and force independent movement parameters? Preparation- and movement-related neuronal activity in the monkey cortex. *Exp Brain Res* 99: 56–74, 1994.
- Riehle A and Requin J.** Monkey primary motor and premotor cortex: single-cell activity related to prior information about direction and extent of an intended movement. *J Neurophysiol* 61: 534–549, 1989.
- Riehle A and Requin J.** The predictive value for performance speed of preparatory changes in neuronal activity of the monkey motor and premotor cortex. *Behav Brain Res* 53: 35–49, 1993.
- Rosenbaum DA.** Human movement initiation: specification of arm, direction, and extent. *J Exp Psychol Gen* 109: 444–474, 1980.
- Santhanam G, Ryu SI, Yu BM, Afshar A, and Shenoy KV.** A high-performance brain-computer interface. *Nature* 442: 195–198, 2006.
- Scott SH and Kalaska JF.** Reaching movements with similar hand paths but different arm orientations. I. Activity of individual cells in motor cortex. *J Neurophysiol* 77: 826–852, 1997.
- Scott SH, Sergio LE, and Kalaska JF.** Reaching movements with similar hand paths but different arm orientations. II. Activity of individual cells in dorsal premotor cortex and parietal area 5. *J Neurophysiol* 78: 2413–2426, 1997.
- Shen L and Alexander GE.** Neural correlates of a spatial sensory-to-motor transformation in primary motor cortex. *J Neurophysiol* 77: 1171–1194, 1997a.
- Shen L and Alexander GE.** Preferential representation of instructed target location versus limb trajectory in dorsal premotor area. *J Neurophysiol* 77: 1195–1212, 1997b.
- Shenoy K and Churchland M.** Subthreshold microstimulation of PMd, but not M1, increases reaction time. *Soc Neurosci Abstr* 603.6, 2004.
- Shenoy K, Churchland M, Santhanam G, Yu B, and Ryu S.** Influence of movement speed on plan activity in monkey pre-motor cortex and implications for high-performance neural prosthetic systems design. *IEEE EMBS Annu Mtg* 1897–1900, 2003a.
- Shenoy KV, Meeker D, Cao S, Kureshi SA, Pesaran B, Buneo CA, Batista AP, Mitra PP, Burdick JW, and Andersen RA.** Neural prosthetic control signals from plan activity. *Neuroreport* 14: 591–596, 2003b.
- Snyder LH, Batista AP, and Andersen RA.** Coding of intention in the posterior parietal cortex. *Nature* 386: 167–170, 1997.
- Tanji J and Evarts EV.** Anticipatory activity of motor cortex neurons in relation to direction of an intended movement. *J Neurophysiol* 39: 1062–1068, 1976.
- Todorov E and Jordan MI.** Optimal feedback control as a theory of motor coordination. *Nat Neurosci* 5: 1226–1235, 2002.
- van Beers RJ, Haggard P, and Wolpert DM.** The role of execution noise in movement variability. *J Neurophysiol* 91: 1050–1063, 2004.
- Weinrich M and Wise SP.** The premotor cortex of the monkey. *J Neurosci* 2: 1329–1345, 1982.
- Weinrich M, Wise SP, and Mauritz KH.** A neurophysiological study of the premotor cortex in the rhesus monkey. *Brain* 107: 385–414, 1984.
- Wise SP.** The primate premotor cortex: past, present, and preparatory. *Annu Rev Neurosci* 8: 1–19, 1985.
- Wise SP and Kurata K.** Set-related activity in the premotor cortex of rhesus monkeys: effect of triggering cues and relatively long delay intervals. *Somatosens Mot Res* 6: 455–476, 1989.
- Zipser D and Andersen RA.** A back-propagation programmed network that simulates response properties of a subset of posterior parietal neurons. *Nature* 331: 679–684, 1988.