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Neural Correlates of Reaching Decisions in Dorsal Premotor Cortex: Specification of Multiple Direction Choices and Final Selection of Action

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Summary

We show that while a primate chooses between two reaching actions, its motor system first represents both options and later reflects selection between them. When two potential targets appeared, many (43%) task-related, directionally tuned cells in dorsal premotor cortex (PMd) discharged if one of the targets was near their preferred direction. At the population level, this generated two simultaneous sustained directional signals corresponding to the current reach options. After a subsequent nonspatial cue identified the correct target, the corresponding directional signal increased, and the signal for the rejected target was suppressed. The PMd population reliably predicted the monkey's response choice, including errors. This supports a planning model in which multiple reach options are initially specified and then gradually eliminated in a competition for overt execution, as more information accumulates.

Introduction

Animals are continuously faced with multiple opportunities for action and must make decisions about which action to perform at any given moment. Besides deciding *what* to do, an animal must also specify *how* to execute the action by defining the metrics of the movement on the basis of spatial information. This could be accomplished in strict serial order by first making an abstract decision about what action to take and then performing the sensorimotor transformations that specify its spatial and temporal metrics. Alternatively, the motor system could begin to specify the metrics of several potential actions based on sensory information, while at the same time weighing the likelihood, costs, and benefits of each, before arriving at a decision. Sensory information about the possible range of metrics of multiple potential actions is always available (Gibson, 1979). For example, the spatial location, size, and orientation of multiple objects delimit a range of actions to reach and grasp one of them. From this perspective, the process of sensory analysis of the world generates not only a facsimile of its structure but also a pragmatic representation of the action opportunities the world makes available (what Gibson [1979] called "affordances"). Decision-making underlying voluntary behavior can then be viewed at least in part as the process of selecting from this pragmatic representation of motor options the one that will be released into overt execution.

This pragmatic outlook predicts that decision-making processes will be largely embedded within the neural systems traditionally associated with motor control. This is motivated by evolutionary considerations. Animals evolved in a world of real-time situated activity, and the appropriate selection of actions was likely the primary context and driving force within which decision-making processes evolved. Even the abstract cognitive abilities of humans do not appear to be completely free from the influence of an action-centered heritage (Hommel et al., 2001).

Consistent with this prediction, neuronal correlates of saccadic decision-making processes are found in many of the brain structures involved in saccade generation (Basso and Wurtz, 1998; Ditterich et al., 2003; Glimcher, 2003; Gold and Shadlen, 2001; Hasegawa et al., 1998; Ito et al., 2003; Platt and Glimcher, 1999; Schall and Thompson, 1999; Shadlen and Newsome, 2001). However, the eye is a sensory organ, and where one looks is normally determined by how one samples visual information about the world (Yarbus, 1967). Furthermore, in the natural world outside of neurophysiological laboratories, eye movements almost never directly lead to behaviorally relevant outcomes such as juice rewards. The eye may therefore be a special case in which a close association of perceptual, decisional, and motor processes reflects its unique sensory role. There is no reason to assume that this close association must exist for effectors such as the arm, whose main role is physical interaction with the world. Nevertheless, studies of tactile perceptual decisions suggest a similar functional architecture for the limb motor system (Hernandez et al., 2002; Romo et al., 2002, 2004).

Another prediction is that the motor system can generate simultaneous early representations of a limited number of potential actions before choosing one to execute. Decision-making models of response choice often assume that separate parallel circuits accumulate evidence for each of the competing choices (Carpenter and Williams, 1995; Glimcher, 2003; Mazurek et al., 2003; Ratcliff et al., 2003; Smith and Ratcliff, 2004). Behavioral results also support the existence of simultaneous encoding. For example, the trajectory of a reach to a target is influenced by the presence and placement of distracters (Tipper et al., 1998; Welsh et al., 1999), suggesting that multiple target- and distracter-related directional signals coexist in neural populations specifying reach direction (Tipper et al., 2000).

The movement direction-related activity of neural populations is preshaped by partial information on possible motor choices (Basso and Wurtz, 1998; Bastian et al., 2003; Kurata, 1993; Munoz and Wurtz, 1995; Riehle and Requin, 1989). Bastian et al. (2003) showed that the directional bias of motor cortical activity is strongly modulated by the degree of certainty about potential target locations before the final target is identified. This supports the view that populations of cells in the motor system can encode a distribution of potential parame-

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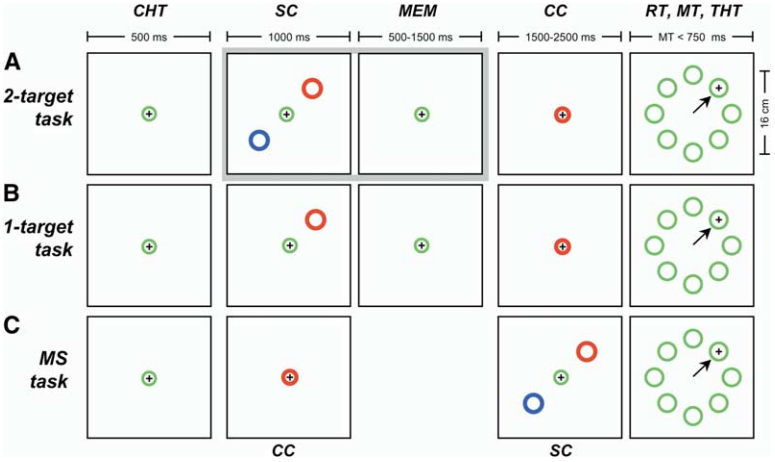

Figure 1. Behavioral Tasks

Replicas of the monitor screen showing the cursor ("+") and sensory cues presented during each epoch in a single trial. (A) Two-target task. From left to right, center-hold, spatial-cue, memory, color-cue, and GO stimuli. The GO signal instructed the monkey to move to the selected target (arrow). See Experimental Procedures for more detail. (B) One-target task. Task epochs were identical to the two-target task except that only one spatial cue appeared during SC, always matching the color of the CC. (C) Match-to-sample (MS) task. Stimulus events were similar to the two-target task except that the CC preceded the SC, and there was no MEM epoch.

ter values for multiple response options, rather than only the specific value of the parameters of a single movement (Cisek, 2001; Erlhagen and Schöner, 2002; Tipper et al., 2000). However, those studies did not examine whether distinct signals coexisted for each potential action.

We report here that neurons in primate dorsal premotor cortex represent simultaneously the directions of two potential reach targets and later reflect the selection of the action to execute. Some of these data have appeared previously in preliminary form (Cisek and Kalaska, 2002b).

Results

Behavioral Results

Monkeys performed instructed-delay tasks in which a single reach target was presented at the beginning of the delay period (one-target task) or two potential targets were presented, one of which was later selected by a nonspatial cue (two-target task). Task details are described in Experimental Procedures and Figure 1. In the two-target task (Figure 1), the correct target was selected in 75% of the trials by monkey Y and in 96% by monkey Z.

Both monkeys spontaneously developed similar patterns of eye movements that indicated that they attended to the salient information provided by the tasks (see the Supplemental Data available with this article online, Figure S7). When the spatial cues appeared in the two-target task, the monkeys briefly gazed at one or both of them or made several saccades between them. During the subsequent MEM epoch, they tended to fixate the central cue until the salient central color cue appeared. In contrast, they did not fixate the central target in the MEM epoch of the one-target task, in which the central color cue provided no salient information. After the color cue in the two-target task, the monkeys looked around more freely, but with a clustering of fixations near the intended target location. After the GO signal in both tasks, both monkeys fixated the target until the cursor entered it.

PMd Activity Reflects Progressive Stages in the Specification and Selection of Movement

Activity was recorded in at least one task from 304 cells in dorsal premotor cortex (PMd; 152 each in monkeys Y and Z) and 58 cells in primary motor cortex (M1; 18 in Y, 40 in Z). The PMd cells were divided into rostral (147 cells) and caudal (157 cells) groups relative to the genu of the arcuate sulcus. A total of 258 PMd and 39 M1 cells were studied in both the two-target and one-target tasks. Most cells (95%) displayed one of four patterns of unimodal or bimodal directional tuning during the SC and CC periods of the two-target and one-target tasks (bootstrap test, $p < 0.01$; see Experimental Procedures). This classification delineates regions along a continuum of properties across the cell sample rather than distinct cell groups. A separate quantitative test of the fit of cell tuning curves to unimodal and bimodal sinusoidal functions (see the Supplemental Data) illustrated the continuous nature of response properties and confirmed that the discrete bootstrap classification procedure delineated meaningful regions within this continuum in an acceptably conservative manner.

Movement (*M*) *cells* (51/297, 17%) were not directionally tuned during the SC or CC epoch in either the two-target or one-target tasks and were unimodally tuned only after the GO signal. They were more common in M1 (14/39, 36%) than in PMd (33/258, 13%). *Buildup* (*BU*) *cells* (58/297, 20%) were not directionally tuned during the SC epoch of either task, but showed a gradual growth of unimodal tuning throughout the CC epoch of both tasks prior to the onset of the GO signal (Figures 2A and 2B). Build-up activity prior to a GO signal has been described in M1 and PMd (Riehle and Requin, 1989) and is also common in the oculomotor system (Bruce and Goldberg, 1985; Hanes and Schall, 1996; Munoz and Wurtz, 1995).

Selected-response (*SR*) *cells* (46/297, 15%) became directionally tuned as soon as unambiguous information was provided on the correct target in all tasks (Figures 2C and 2D). They became unimodally tuned when the single spatial cue appeared at the onset of the SC epoch in the one-target task (Figure 2C). In contrast, in the two-target task, SR cells showed little or no re-

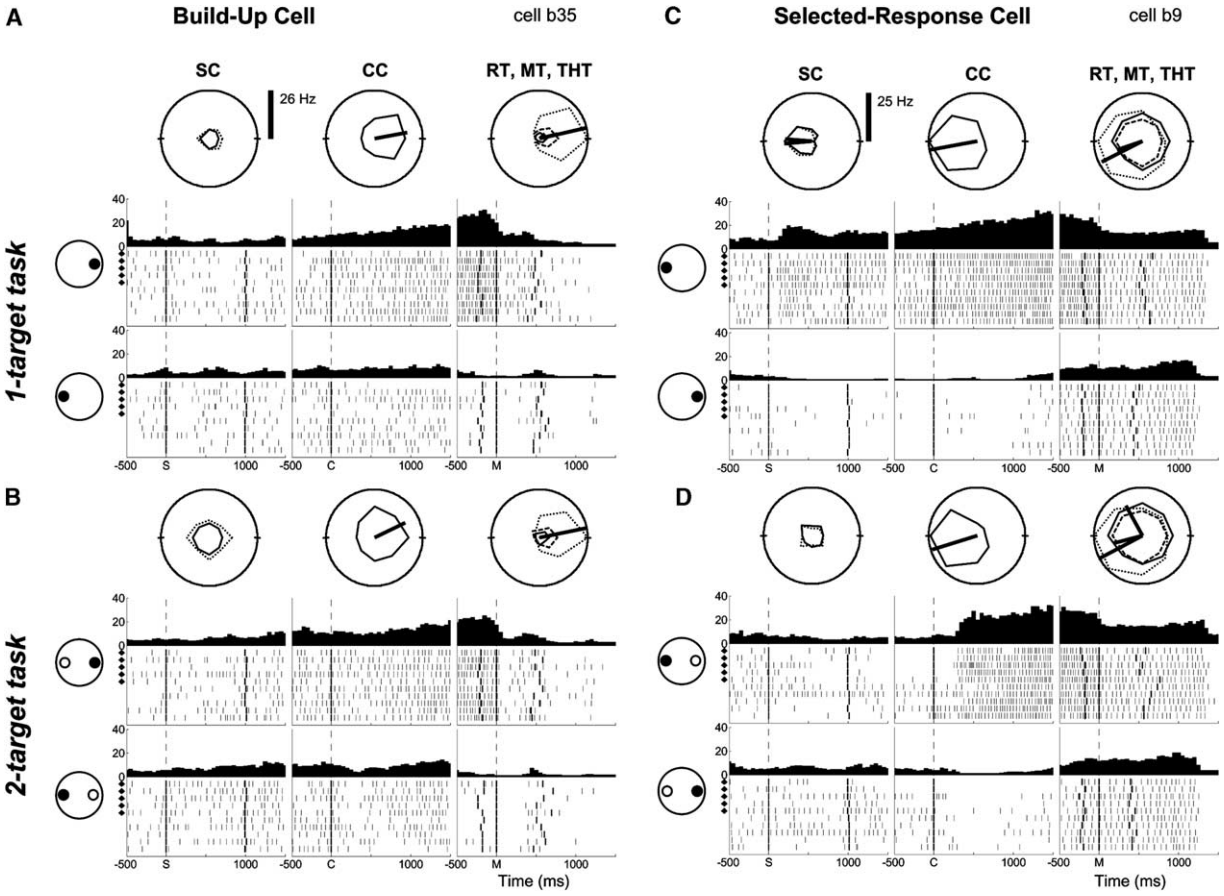

Figure 2. Example Build-Up and Selected-Response Cells

(A and B) Responses of a build-up cell in the one-target (A) and two-target (B) tasks. The upper rasters and histograms show activity during trials at the cell's PD, and the lower rasters and histograms show activity in the OD. Rasters and histograms are aligned on spatial cue onset (S), color-cue onset (C), and movement onset (M). Thick ticks in raster lines indicate spatial cue onset, spatial cue offset, color cue onset, GO onset, movement onset, and movement end. Circular diagrams to the left of the rasters show locations of the spatial cues and the selected target (filled), and diamonds indicate trials in which the selected target was red. Circular diagrams above the histograms show the tuning curves of the cell for all target directions in each epoch: spatial cue, color cue, and target-hold time (solid lines), memory, reaction time (dotted lines), and movement time (dashed lines). Thick vectors indicate the PD of significantly directional tuning curves.

(C and D) Responses of a selected-response cell during the one-target (C) and two-target (D) tasks, in the same format.

sponse to the onset of the two spatial cues and were not directionally tuned during the SC epoch, but became unimodally tuned once the nonspatial color cue indicated which of the previous spatial cues was the selected target (Figure 2D).

The largest group was *potential-response* (*PR*) *cells* (127/297, 43%) (Figure 3). Like SR cells, most PR cells became unimodally tuned in response to the single spatial cue in the one-target task (Figure 3A). Unlike SR cells, however, PR cells also discharged whenever either of the two spatial cues of the two-target task appeared near their preferred direction, even though the cues provided ambiguous information about the final target (Figure 3B). This yielded bimodal tuning functions in the two-target task when trials were sorted according to the final selected target (bootstrap test, $p < 0.01$). Most PR cells (102/127, 80%) exhibited bimodal tuning during the SC period, which was sustained during the MEM epoch by 60 PR cells. The remaining 25 PR cells (20%) only showed significant bimodal tuning during the MEM epoch. When the nonspatial color cue appeared in the two-target task, most PR cells (107/127, 84%) rapidly became unimodally tuned as a function of the memorized location of the earlier spatial cue with the matching color (Figure 3B). This unimodal tuning during the CC epoch of the two-target task was similar to their tuning in the one-target task.

The response of single PR cells to a spatial cue at their PD in the one-target task was significantly reduced when a second spatial cue appeared simultaneously in the opposite direction (OD) in the two-target task (Figure 4A; paired t test, $p < 10^{-5}$). The responses were significantly smaller than the linear sum of their responses to the single cues presented at the PD and OD in the one-target task (i.e., two-target response < response to PD + response to OD; paired t test, $p < 10^{-10}$) or the sum of the changes from background activity [i.e., two-target response < baseline + (response to PD − baseline) + (response to OD − baseline); $p < 10^{-6}$]. This suggests that PR activity during the SC ep-

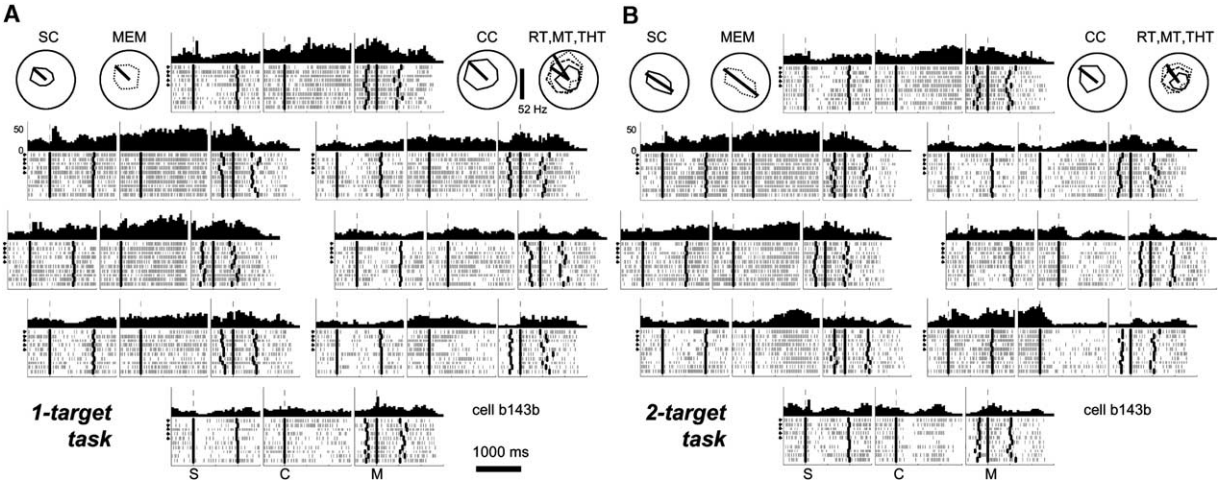

Figure 3. Example Potential-Response Cell

Responses of a single PR cell for all eight directions in the one-target (A) and two-target (B) tasks. The rasters and histograms for each direction are formatted as in Figure 2.

och of the two-target task is not a simple passive response to two stimuli, but presumably reflects other factors.

Furthermore, when normalized to the maximum activity in each task, the width of the two-target tuning function during the SC epoch was typically narrower than in the one-target task for most PR cells (Figures 4B and 4C; paired t test, $p < 10^{-4}$). Thus, the bimodal tuning function of PR cells in the two-target task was not simply an overlay of two copies of its unimodal tuning function in the one-target task. This "pinching-in" of the bimodal tuning function may reflect competitive interactions between cells with different tuning preferences.

Cortical Gradient of Cell Response Properties

The four cell-response types were distributed nonuniformly across the region of cortex studied (Figure 5). Most M1 cells were either M (15/39, 38%) or BU cells (17/39, 44%), whereas they were a minority in PMd (36/258, 14%, and 41/258, 16%, respectively). SR (3/39, 8%) and PR (3/39, 8%) cells were present but rare in M1, but were common in PMd (43/258, 17%, and 124/258, 48%, respectively). Of the 124 PR cells in PMd, 76 (61%) were rostral to the genu of the arcuate sulcus. Although there was a bias in sampling toward the part of PMd around the genu of the arcuate, the data suggest a rostro-caudal gradient of cell properties (Figure 5B). This trend was observed in each recording chamber in each monkey (data not shown).

Our penetrations spanned the border between the rostral (F7, pre-PMd) and caudal (F2, PMd proper) parts of PMd (Matelli et al., 1998; Picard and Strick, 2001). We injected the retrograde tracer Texas Red into the cortical locus of our most rostral penetrations in the right hemisphere of monkey Z (Figure 5A). Labeled cells were found in parietal area PGm but not in PEip or in M1 (data not shown). This connectivity suggests that our most rostral penetrations had encroached the caudal part of F7 or pre-PMd. Many other penetrations were in caudal PMd (F2, or PMd proper) and extended into M1 (Figure 5A), and SR and PR cells were distributed in gradient fashion throughout the sampled area.

In summary, there was a trend for cells in the rostral part of the sampled region to become active as soon as potential targets were presented. Cells in more caudal regions were mainly activated only after information was given to select the target or to initiate the movement, but with considerable overlap of response properties along the rostro-caudal axis (Crammond and Kalaska, 2000; Johnson et al., 1996).

Population Activity Reflects Parallel Specification of Two Potential Targets and Selection between Them

The rostral and caudal PMd populations both emitted a strong unimodal directional signal as a function of spatial cue location in the one-target task (Figure 6A). A short-latency phasic response was followed by a tonic response whose intensity increased gradually throughout the SC, MEM, and CC epochs, with no additional response component at the time of color cue presentation (see Figure S6).

When two potential targets appeared in the SC epoch of the two-target task, two discrete directional signals arose simultaneously that were stronger in rostral than caudal PMd (Figure 6B). There was evidence of a concurrent nondirectional suppression of activity in M1 (Figure 6B). When the central color cue identified the selected target, PMd activity changed abruptly to a unimodal pattern oriented in the selected direction. There was a sharp increase in the activity of cells tuned toward the selected target and a rapid suppression of cells tuned toward the other target in both rostral and caudal PMd (Figure S6). Unimodal tuning emerged more gradually in M1 before the GO signal in both tasks.

When monkeys performed a variant of the two-target task in which the cues were 90° apart, activity again reflected the presence and relative location of both

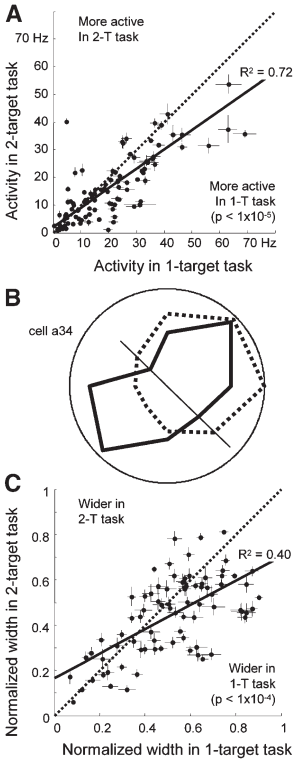

Figure 4. Effect of the Number of Spatial Cues on PR Cell Activity during SC Epoch

(A) Scatter plots of the discharge rate from 100–250 ms after spatial cue onset for single PR cells in the one-target (x axis) and two-target (y axis) tasks. Dots and lines show the mean and standard error of single-trial responses.

(B) Tuning functions of a single PR cell during the SC epoch of the one-target (dotted line) and two-target (solid line) tasks. Thin line indicates the directions orthogonal to the PD, which were used to compute width.

(C) Normalized widths of the SC tuning functions of all PR cells, shown as mean and standard error for one-target and two-target tasks.

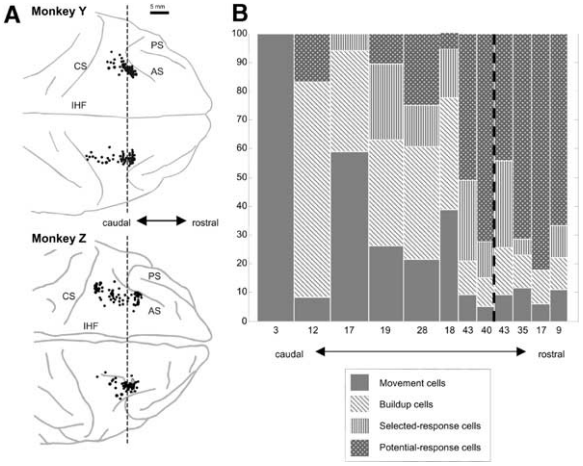

Figure 5. Anatomical Distribution of Recorded Cells

(A) Locations of electrode penetrations in PMd of monkeys Y and Z. CS, central sulcus; AS, arcuate sulcus; PS, principal sulcus; IHF, interhemispheric fissure; gray oval, injection sites of Texas Red tracer in the right hemisphere of monkey Z.

(B) Rostro-caudal distribution of the four cell classes in the cortex. The five leftmost bins are 2 mm across, all others are 1 mm. Numbers below the bins indicate the number of cells recorded in that part of cortex. Vertical dashed line, location of the genu of the arcuate sulcus.

cues (middle and right panels in Figure 6C). Only four of the eight directions were used in this variant, so it is not clear whether the population activity in Figure 6C contained two distinct directional signals or only a single broad plateau of activity (Bastian et al., 1998).

The two opposing directional signals during the SC period of the two-target task could be an artifact of pooling trials in which the monkeys randomly guessed one way or the other with equal probability. The guess would be confirmed by the color cue or be contradicted, requiring a switch in plan. Analysis of the moment-to-moment variability of activity during trials in which spatial cues appeared at the PD and OD argued strongly against a "guess-and-switch" strategy and supported two concurrent signals (see the Supplemental Data).

Cells Respond Primarily to Novel Information about Direction

The color of the spatial cue and the later color cue were always the same in each trial of the one-target task and provided no behaviorally salient information. Differential responses to cue color were rare in the one-target task (main effect of color in <1% of cells during SC, <2% during CC, ANOVA, $p < 0.01$). In contrast, the location-color conjunctions of the spatial cues and the color of the nonspatial color cue were critical to successful performance in the two-target task. Cells often showed a directionally tuned response to the onset of the color cue in the two-target task (Figures 2 and 3), but still rarely showed a color-selective response to any of the cues (main effect of color in <2% of cells in SC, <3% in CC, ANOVA, $p < 0.01$). This suggests that the cells were primarily processing novel salient information provided by the cues about the spatial metrics of the task.

To assess this further, 87 cells (45 PR, 12 SR, 21 BU, 5 M, 4 unclassified) were tested in a match-to-sample (MS) task in which the order of spatial and color cues was reversed (Figure 1C). The initial color cue was highly salient but could not be associated with any movement direction. During the ensuing SC epoch, the two spatial cues were identical to those in the two-target task. However, whereas they ambiguously specified two equally likely potential targets in the two-target task, they unambiguously specified one target in the MS task because of the prior knowledge provided by the preceding color cue.

No tested PMd cell responded to the onset of the color cue in the MS task, even though it was highly salient (CC epoch, main effect of color; ANOVA, $p < 0.01$). This contrasted with the strong directional response of PR and SR cells to the color cue in the two-target task, which could be associated with the memorized location of the color-matched spatial cue to specify direction. Instead, there was a modest nondirectional and non-color-specific ramp increase in activity during the CC

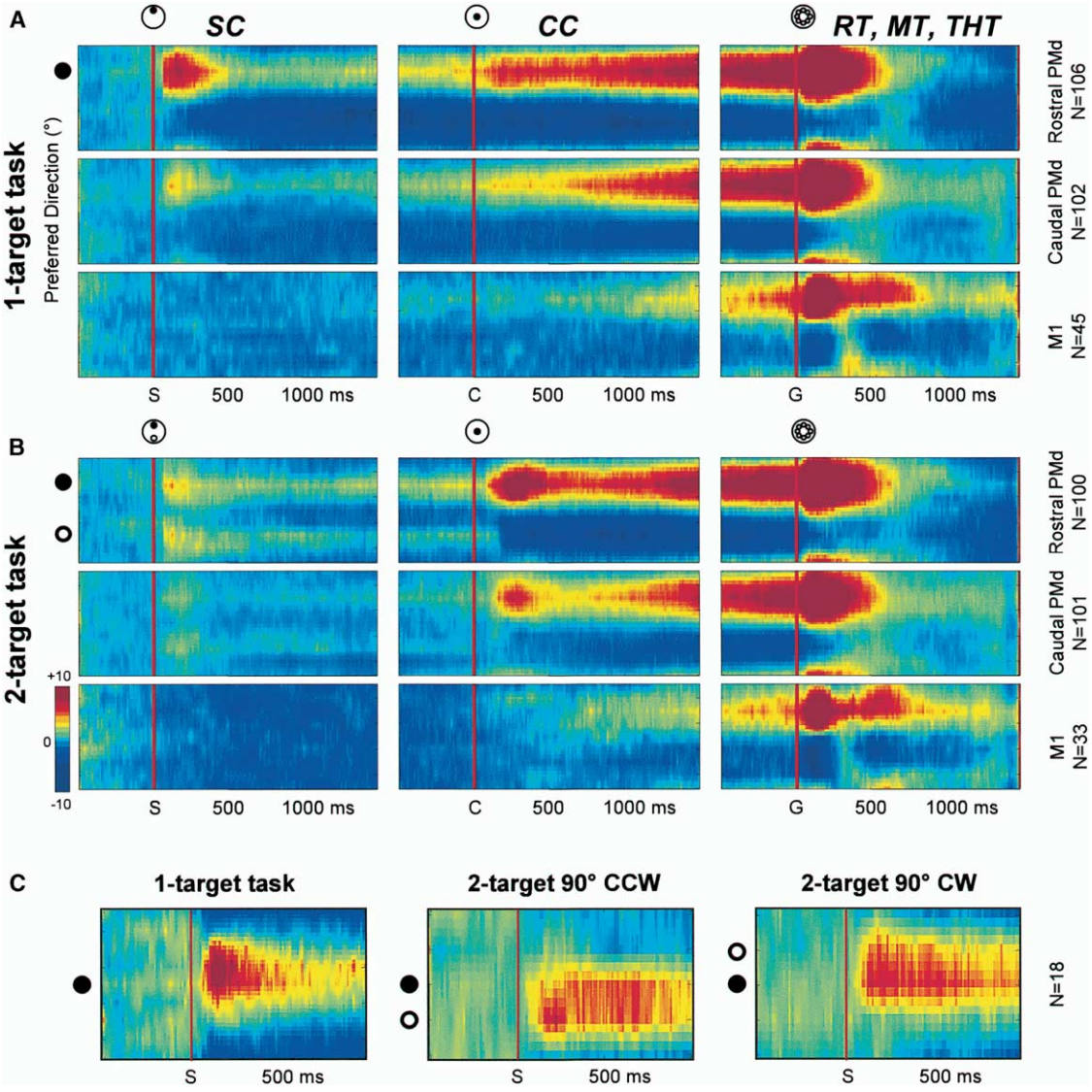

Figure 6. Population Activity in PMd and M1

Population activity in one-target (A) and two-target (B) tasks represented as color contour plots for cells in rostral PMd, caudal PMd, and M1. In each row, panels are aligned on spatial cue onset (S), color-cue onset (C), and GO signal onset (G). In each panel, each horizontal row represents the average activity of cells whose PD lies at a given angle from the direction of the selected target (filled circle on left). Color indicates change in firing rate relative to the background rate of each cell sample during the 500 ms prior to spatial cue onset (scale on left). (C) Contour plots of PMd activity recorded in the 90° variant of the two-target task. (Left) SC activity in the one-target task. (Middle) SC activity when a second spatial cue appeared 90° CCW from a cue in each cell's PD. (Right) SC activity when a second spatial cue appeared 90° CW from the PD.

period (Figure 7B), possibly in anticipation of the arrival of the salient SC cues (Crammond and Kalaska, 1996; Vaadia et al., 1988).

When the two spatial cues appeared in the SC epoch of the MS task, the activity of 70/87 cells (80%) was unimodally tuned when averaged over the SC epoch, 5 (6%) were bimodally tuned, and 12 (14%) were untuned. Strikingly, 40/45 PR cells (89%), which were *bimodally* tuned during the SC epoch of the two-target task (Figure 3B), were *unimodally* tuned in response to the same cues in the MS task (Figure 7A). They signaled the location of the spatial cue that was designated as the target by the prior color cue, and not the other spatial cue during most of the SC epoch. Only 3 (7%) PR cells were bimodally tuned in both two-target and MS tasks. The spatial cues did not evoke a directional response in SR and BU cells in the two-target task, but evoked a unimodal response in 28/33 (85%) of them in the MS task. The unimodal response in the SC epoch of the MS task was stronger than the bimodal SC response in the two-target task, suggesting that cell activity reflected the quality of the directional information provided by the cues, not their physical properties. Nevertheless, a minority of cells showed a main effect

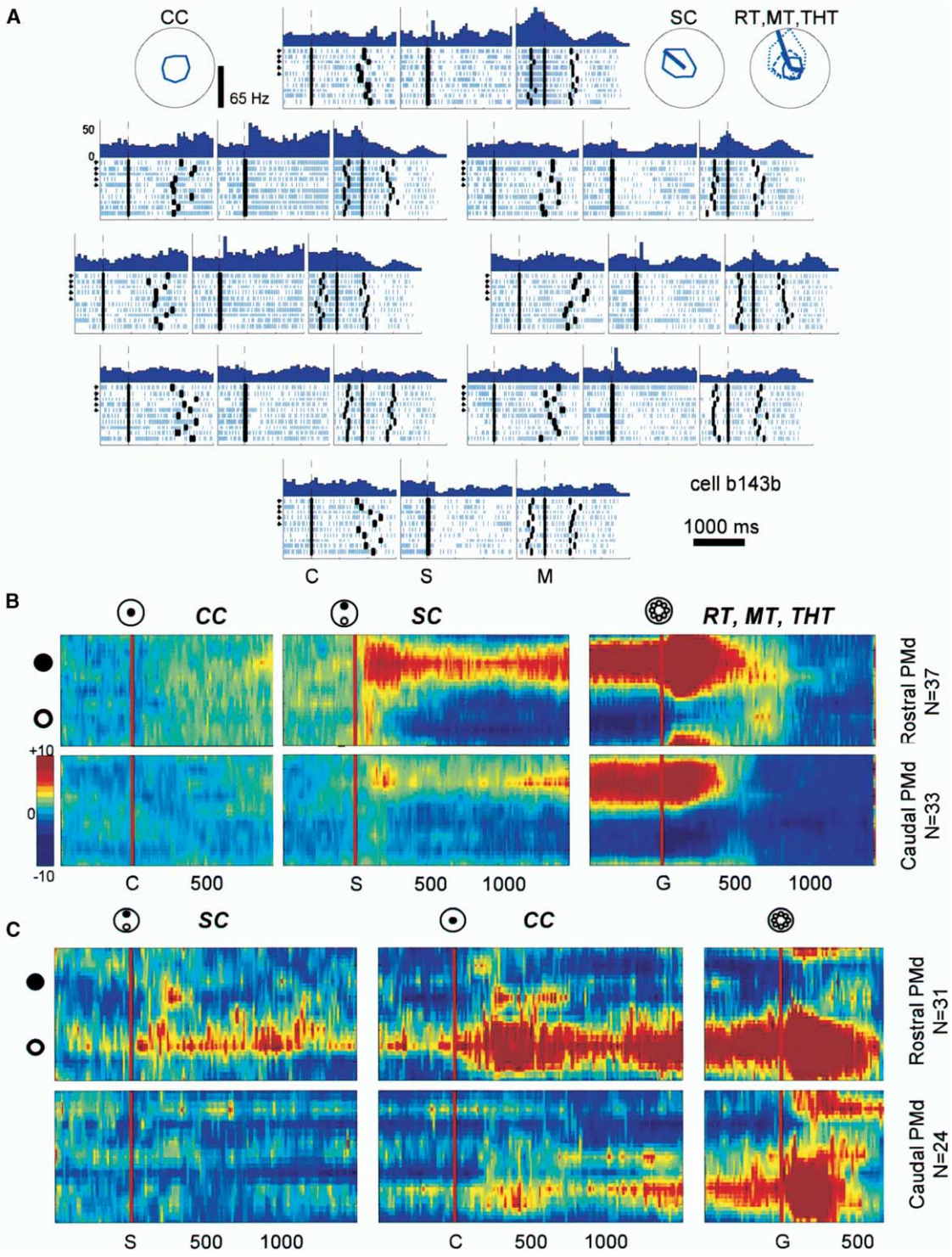

Figure 7. Activity during the MS Task and Error Trials

(A) Responses of a PMd cell in the MS task. Same cell and format as Figure 3.

(B) Population activity in the MS task. Same format as Figure 6.

(C) Population activity during error trials in the two-target task.

of color during the SC epoch of the MS task (15/87, 17%, ANOVA, $p < 0.01$), even though it could be associated with a particular movement direction.

The average activity of rostral and caudal PMd populations was unimodally tuned during most of the SC period of the MS task (Figure 7B). However, a brief ini-

tial burst to the unselected target was evident, especially in the rostral population. A clear transient bimodal response was also seen in a few single PR cells (e.g., Figure 7A, upper left and lower right targets). This shows that the PMd population transiently signaled the location of both spatial cues in the MS task, one of which was then quickly rejected as a movement target.

These MS task results further show that PMd cells do not simply code the physical properties of salient stimuli. Instead, they represent the information provided by those cues about the spatial metrics of potential motor outputs in the context of the current task and trial.

PMd Activity Predicts Response-Choice Errors

The CC epoch activity in PMd reliably predicted when monkeys would perform a choice error and move to the wrong target in the two-target task, at both single-cell and population levels (Figure 7C). Identical cue sequences evoked opposite directional responses when they were interpreted correctly or incorrectly (Figures 6B and 7C). The mean activity of PMd cells during the CC of error trials when they incorrectly moved to the preferred target of each cell (14.6 ± 1.5 Hz) was similar to the CC activity when they correctly chose the preferred target (12.6 ± 0.6 Hz). Strikingly, a bias toward the wrong choice was already evident during the SC epoch and possibly even during CHT, especially in rostral PMd. The error-trial results show again that PMd activity reflects how the monkeys interpret the motor instructional content of salient cues, not their physical attributes.

Latency of Neural Processing in Dorsal Premotor Cortex

To measure the latency at which PMd activity reflected the directional information provided by the spatial cue in the one-target task, we calculated the time at which a cell's activity in PD trials exceeded its activity in OD trials (Figure 8A, top). About 40% of cells responded differentially within 100 ms of spatial cue onset. The median latency of PR cells (113 ms) was shorter than the median latency of SR cells (152 ms), but the distributions were not significantly different (KS test, $p > 0.1$). The distribution of latencies of rostral cells (median 98 ms) was significantly lower (KS test, $p < 0.05$) than that of caudal cells (median 147 ms; Figure 8A, bottom). In the two-target task, unambiguous directional information was provided by the color cue. The median latency of the unimodally tuned CC response was 180 ms for PR cells and 182 ms for SR cells (KS test, $p > 0.1$) (Figure 8B, top). Once again, there was a significant difference (KS test, $p < 0.05$) between the distributions for the rostral (median 182 ms) versus caudal cells (median 212 ms) (Figure 8B, bottom).

Response latencies were also calculated for the pooled population data from the 44 cells that were tested in the one-target, two-target, and MS tasks (Figures 8C–8F). These latencies were likely dominated by the timing of the responses of the earliest single cells. The population signal in the one-target task differed between the PD and OD trials 50 ms after the appearance of spatial cues and discriminated the PD from the orthogonal directions at 70 ms (Figure 8C). In the two-target task, the population discriminated PD from orthogonal trials within 80 ms of spatial cue onset (Figure 8D). After the color cue appeared in the two-target task, the population discriminated PD versus OD within 110 ms (Figure 8E). Thus, the response to direct spatial information appears to be very fast and considerably faster than the response to information of a more abstract nature that requires discrimination of color and recollection of remembered color-location conjunctions. The same latency difference was also observed in the MS task (Figure 8F). After the spatial cues appeared, there was both an early response to direct spatial information (the population discriminated PD versus orthog-

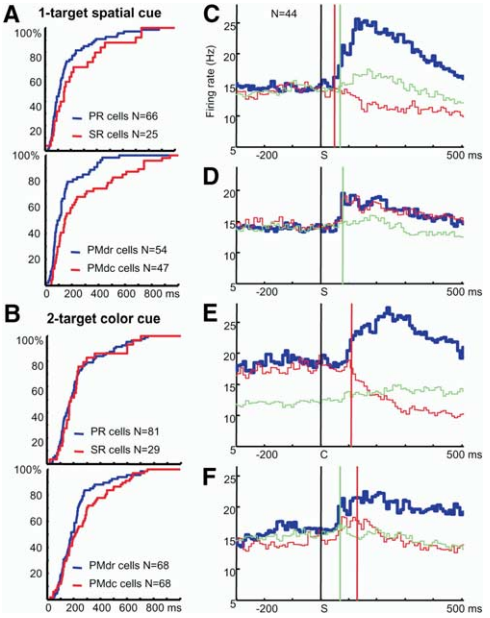

Figure 8. Latencies

(A) Cumulative distributions of latencies at which single cells signal the presence of a spatial cue near their PD. (Top) PR (blue) and SR (red) cells. (Bottom) Rostral (blue) and caudal (red) cells. (B) Cumulative distributions of latencies at which cells discriminate whether the color cue signals a movement in their PD or in the OD. (Top) PR and SR cells. (Bottom) Rostral and caudal cells. Only cells with significant directional tuning and differential response latency are included. (C) Mean population responses aligned to the onset of the spatial cue in each cell's PD (thick blue line), the OD (red), or the orthogonal directions (green) in the one-target task. Vertical red line, latency (50 ms) when the population discriminated a spatial cue at PD from the OD. Green line, latency (70 ms) when the population discriminated a spatial cue at the PD from orthogonal directions. (D) Mean population responses to spatial cue onset in the two-target task. Green line, latency (80 ms) when the population discriminated spatial cues at the PD/OD from the orthogonal locations. (E) Mean population responses to color cue onset in the two-target task. Red line, latency (110 ms) at which the population discriminated whether the color cue selected the PD or OD as the target. (F) Mean population responses to spatial cue onset in the MS task. Green line, latency (70 ms) at which the population discriminated the spatial cues at the PD and OD from orthogonal locations; red line, latency (130 ms) at which the population discriminated whether spatial cues at the PD or OD matched the previous color cue. In (C)–(F), only cells recorded in all three tasks (n = 44) were used.

onal trials in 70 ms) and a later response that reflected the resolution of the color-location conjunction (the population discriminated PD versus OD in 130 ms).

Discussion

Simultaneous Encoding of Multiple Movement Options

This study showed that when monkeys faced two potential reaching targets, directional signals reflecting both options arose in PMd. The signals were discrete and separate when the targets were far apart, but could merge into a continuous pattern when closer together (Bastian et al., 2003). When new information was given to select one target, the corresponding directional signal increased while the other was suppressed. The processes of simultaneous specification of competing options, selection of one over the other, and execution of the selected action were distributed in a continuous rostro-caudal gradient extending from the caudal part of rostral PMd into M1. Single-cell response properties also formed a continuum that could be divided into meaningful categories.

Potential response (PR) cells were active whenever a cue near their preferred direction was a potential reaching target, even if another target was also present elsewhere, either 90° or 180° away, and independent of the color-location conjunctions or the temporal order of the information that determined the final target. The presence of competing options modulated the response of PR cells to potential targets at their PD, which was usually stronger when it was the only available option.

The behavior of PR cells in the two-target task does not imply that single cells initially signaled two opposing movement directions during the SC epoch and then one direction during the CC epoch. A more parsimonious interpretation is that the underlying tuning function of each PR cell was unimodal and signaled the presence of a potential target in its PD. The apparent initial bimodal tuning in the two-target task was a consequence of sorting trials according to the final selected target, including trials in which the cell's preferred target was ultimately rejected. It was the pooled activity of PR cells with different preferred directions that signaled the directionality of the two potential actions during the SC and MEM epochs (Figure 6) (Cisek and Kalaska, 2002b). After the color cue appeared, both PR and SR cells quickly signaled whether or not it designated the previous spatial cue at each cell's PD as the movement target.

Nothing about the task design encouraged or required the simultaneous specification of two movement directions during the SC period. The monkeys could have withheld all motor planning processes until they were given all the information needed to select one target. In theory, they could have stored the color-location conjunctions of the spatial cues in a general-purpose working memory buffer, retrieved that information after the color cue appeared, and initiated motor planning processes only after a decision was reached. The lengthy CC period provided ample time to perform those processes. Alternatively, the monkeys could have used a "guess-and-switch" strategy, arbitrarily planning a response to one of the spatial cues and then switching to the other if the color cue required it. However, analyses of discharge variability argue against this strategy (see the Supplemental Data). Instead, the data suggest that the monkeys simultaneously generated two distinct and mutually exclusive directional signals in PMd when the targets were in opposite directions.

Interpretational Issues

We have interpreted the PMd activities reported here as representations of the potential directions of upcoming voluntary movements. However, it is in principle possible that these activities were instead related to other cortical processes. Here, we examine these alternative interpretations.

Several arguments refute the interpretation that the PMd activity is a neural correlate of sensory processes. First, the activity signaled the directional information in the stimuli, not their presence, since most PR cells maintained or acquired their bimodal tuning after the two spatial cues disappeared in the MEM period. Second, the directionality of CC epoch activity reliably predicted the monkeys' response choice in both correct and error trials, independent of the physical properties of the stimuli that led to the choice. Third, cells did not respond to the color cue in the one-target task, when it provided no new salient information, or in the MS task, when it provided crucial information but had no inherent directional value. Although there was a small increase of activity during CC of the MS task, possibly related to anticipation of the arrival of the SC cues (Crammond and Kalaska, 1996; Vaadia et al., 1988), it was neither directional nor color selective. The cells did respond to the color cue in the two-target task, but only to signal the direction of future movement according to the prior knowledge provided by the spatial cues, independent of the color itself. Fourth, the PMd population signal, including PR and SR cells, was unimodal during most of the SC epoch of the MS task (Figure 7). Even though two stimuli were present, the cells only responded to the one that was designated as the target by the earlier color cue. In the two-target task, PR cells responded bimodally to the identical stimuli and continued after the cues disappeared, while SR cells did not respond at all. Finally, the GO signal, which included a target circle at each possible location, presented a salient stimulus near the preferred direction of each cell in every trial. However, the cells did not respond to the stimuli when prior cues instructed a movement in the opposite direction (Figures 2, 3, and 6).

These findings show that PMd activity primarily signals the information carried by sensory stimuli about the nature and metrics of potential future actions, and not just their presence and features (Wise et al., 1992). This is consistent with a recent study in the frontal eye fields (FEF) (Gold and Shadlen, 2003). The direction of saccades evoked by microstimulation of the FEF while monkeys performed a visual discrimination to select between two saccade targets deviated toward one or the other of them if their locations were known in advance, but did not deviate when they were unknown. Similarly, Wallis and Miller (2003) reported that neural correlates of the identity of complex visual images used

to make a go/no-go decision based on an alternating arbitrary match/nonmatch rule were quite modest in PMd but stronger in prefrontal cortex. Although the identity of the images was critical to the decision process, it had no bearing on the metrics of the motor response—release a lever. In contrast, correlates of the operant rule (match or nonmatch) in each trial and the chosen response (go or no-go) were stronger and earlier in PMd than in PF. All of these results suggest that decision-making processes influence FEF and PMd activity only as far as those processes can be associated with specific motor outputs.

The PMd activity could also be a neural correlate of an abstract working-memory buffer that retains the information needed to make a decision about response choices in this task. However, activity signaling the crucial color information provided by the sensory cues was virtually absent in PMd. Furthermore, a working-memory buffer should be most active when memory and attention loads are the greatest. This should occur during the MEM epoch of the two-target task, when the monkeys had to remember the color-location conjunctions of two prior spatial cues while attending the appearance of a third (color) cue. However, SR, BU, and M cells were inactive at that time, and PR cells were typically less active than during the CC epoch, after the decision was made and memory and attention load were presumably reduced. The strongest activation in PMd in every task was seen after all the cues had been presented and the monkeys could select the direction of movement. These findings argue against a general-purpose working-memory hypothesis. Instead, PMd activity was primarily related to the spatial metrics of potential motor outputs and may represent a form of "prospective code" for impending actions (Rainer et al., 1999).

The monkeys' oculomotor behavior was not controlled, so the PMd signals could have been influenced by gaze-related modulation (Boussaoud et al., 1998; Cisek and Kalaska, 2002a). However, several analyses strongly argue that this could not explain the responses reported here (see the Supplemental Data). In particular, the directional tuning of cell activity recorded only during periods of central fixation exhibited all of the basic features of the data, irrespective of gaze direction.

The PMd activity may have been generated by shifts of overt or covert attention (Lebedev and Wise, 2001). However, when gaze behavior is unconstrained, primates tend to look toward the locus of attention (Kowler et al., 1995; Kustov and Robinson, 1996; Lebedev and Wise, 2001). The weak correlations of cell activity with gaze direction (Cisek and Kalaska, 2002a; see the Supplemental Data, Figure S8) therefore suggest that the direction of overt attention had only a modest effect in this task. Alternatively, the neural activity could have been modulated by covert attention directed at spatial locations of interest. However, this explanation requires that the bimodal tuning of PR cells observed while the monkeys fixated the central target during the MEM period of the two-target task was caused by covert attention divided between two memorized potential peripheral target locations while at the same time looking at and presumably overtly attending an impending color change at the central target. This lacks the appeal of simplicity and seems less plausible than the more parsimonious explanation that the responses signal two potential movement directions. Nevertheless, attention was not directly manipulated in this study and remains a potential factor in the interpretation of the results.

Specification and Selection of Movement Direction

Three kinds of neural responses appear to occur at different latencies, including rapid responses encoding the location of spatial cues, slightly slower activity reflecting the selection of action based on stimulus-response association rules, and gradual build-up of activity prior to movement onset (Sato and Schall, 2003; Schall and Thompson, 1999; Thompson et al., 1996). The earliest responses signaled the location of salient cues and were remarkably fast, 50–60 ms after the onset of spatial cues, given the general assumption that PMd lies near the end of the path from sensory input to motor output. However, other studies have also found widespread activation of multiple cortical regions at short latencies comparable to that observed here, with little evidence of a serial cascade (Schmolesky et al., 1998). Spatial processing along the dorsal visual stream appears to be very rapid (Bisley et al., 2004; Schmolesky et al., 1998) and may not involve only strict transcortical feedforward processing emphasized by serial theories.

In the two-target task, a differential population response signaled the direction of the selected target according to memorized color-location conjunctions 110 ms after the onset of the color cue. Because the conjunctions were fully counterbalanced, the directional response reflected processes beyond simple stimulus classification or responses to the color change itself.

It is interesting to note that in the MS task, similar response latencies were seen after spatial cue onset, despite the reversed order of presentation of cues. When the two spatial cues appeared, the PMd population discriminated their directions within 70 ms, but did not discriminate which one matched the prior color cue until 130 ms after spatial cue onset.

These results suggest that PMd neurons processed information on the direction of upcoming movements in this task in two stages. First, they specified the possible directions indicated by direct spatial information. Next, those directional signals were modulated using information that selected from among the potential actions the one that was most appropriate. This occurred more slowly and presumably involved more complex cortical processing.

Finally, there was a gradual build-up of activity prior to the onset of the GO signal. This build-up may reflect anticipation of the timing of movement initiation and is likely analogous to the build-up activity reported in M1 and PMd (Crammond and Kalaska, 1996; Riehle and Requin, 1989; Vaadia et al., 1988), FEF (Bruce and Goldberg, 1985; Hanes and Schall, 1996), and superior colliculus (Munoz and Wurtz, 1995). This build-up may shorten reaction times by bringing the neural population signal closer to the threshold for initiating the movement (Hanes and Schall, 1996).

The stronger response of PR cells to the appearance of spatial cues at their PD in the one-target task than

in the two-target task (Figure 4) may reflect estimates of prior probability (Basso and Wurtz, 1998; Platt and Glimcher, 1999). Because each task was performed in lengthy blocks of trials, the monkey likely could anticipate how many spatial cues would appear in a given trial and thus how probable its associated movement would be, and this expectation may have modulated PMd activity. Furthermore, cells with different directional preferences may exert an inhibitory influence on each other. This interaction has been inferred indirectly in motor cortex (Georgopoulos et al., 1993). Lateral inhibition is also suggested by the pinching-in of the normalized tuning functions of PR cells in the two-target task compared to the one-target task (Figure 4). When two spatial cues were presented in opposite locations orthogonal to the PD of a given cell, the simultaneous activation of the two populations of cells with PDs in those directions could exert a greater combined lateral inhibition on the activity of the recorded cell than would be generated by a single cue at only one of the locations, causing a pinching-in of the tuning function (Figure 4B).

The presence of two simultaneous directional signals in PMd has several important implications for motor control theories. For example, most computational theories of sensorimotor transformations transform a single point in one coordinate frame into a single point in another (Bullock et al., 1993; Pouget and Snyder, 2000; Salinas and Abbott, 1995). However, our results (see also Bastian et al., 2003) suggest that the population code can represent a distribution of possible values, all of which need to pass through coordinate transformations. This forces revision of the computational theories of how such transformations take place and how they are learned.

Models of Decision Making and Planning

Models of decision making leading to action have been most significantly developed in the oculomotor system (Carpenter and Williams, 1995; Glimcher, 2003; Mazurek et al., 2003; Smith and Ratcliff, 2004). A central concept in these models is a gradual accumulation of evidence for making a given saccade, often expressed in terms of likelihood or Bayesian decision theory (Glimcher, 2003; Gold and Shadlen, 2001). A neural integrator accumulates evidence for a given saccade, which is initiated when the evidence reaches a preset decision threshold (Carpenter and Williams, 1995; Mazurek et al., 2003; Smith and Ratcliff, 2004). The integration begins at a level set by prior knowledge, grows at a rate proportional to the strength of the supporting evidence, and reaches a threshold determined in part by urgency and accuracy demands. With the assumption that these parameters are subject to noise, a great deal of behavioral data on reaction times and error rates can be explained (Carpenter and Williams, 1995; Smith and Ratcliff, 2004). When multiple potential saccadic targets appear, multiple sites become active in LIP (Platt and Glimcher, 1997), FEF (Hommel et al., 2001; Schall and Thompson, 1999; Thompson et al., 1996), and superior colliculus (Basso and Wurtz, 1998). The activity in both superior colliculus (Basso and Wurtz, 1998) and LIP (Platt and Glimcher, 1999) that is related to these potential targets is modulated by the probability of making a saccade in that direction. These results implicate traditionally "motor" structures in the decision-making process. Similar findings have been made in a tactile discrimination task in the arm motor system (Hernandez et al., 2002; Romo et al., 2002, 2004).

The present results can be interpreted in similar terms. PR cells may signal the likelihood that a impending movement will be in their preferred direction based on current evidence, as proposed for MT neurons in a visuomotor task (Mazurek et al., 2003). The weaker responses of PR cells to a spatial cue at their PD in the two-target task than the one-target task may reflect the 50% lower likelihood of an eventual movement in that direction in the former task. SR cells could pool the responses from PR cells with different PDs to determine the relative likelihood of movements in their PD compared to others, as proposed for LIP and PF neurons (Kim and Shadlen, 1999; Mazurek et al., 2003; Shadlen and Newsome, 2001). As a result, SR cells only discharge when evidence favors their preferred option over others. Alternatively, PR cells may accumulate the evidence and SR cells signal the categorical decision reached after one population of PR cells crosses the decision threshold. Categorical decision units have been proposed in some models (Mazurek et al., 2003). They have been reported in the superior colliculus (Glimcher and Sparks, 1992) but not to date in LIP or FEF during oculomotor tasks. Categorical neurons have also been described in ventral premotor cortex, SMA, and M1 during a tactile decision task (Hernandez et al., 2002; Romo et al., 2004). Finally, rather than being distinct serial stages, PR and SR cells may contribute to a single distributed neural integrator in which SR cells occupy a position that is closer to the final decision stage. The present task could not distinguish between these possibilities because the presentation of information was abrupt, location and color discriminations were easy, and the delays imposed by the task confounded any reaction time effects that might have been coupled to temporal integration of evidence to a decision threshold.

Decision theory suggests that simple choices are made through a competition between options. However, questions remain regarding the nature of the representations of the competing options when the decision concerns choices of action. The options may be defined through abstract categorization, and the resulting categories serve as the basis for decision making. Alternatively, this information could be incorporated into early representations of the potential actions, within the neural populations that control a continuous output parameter such as reaching direction. Decision making can then proceed by weighing the evidence for and the estimated payoff from each of those actions. This latter situation makes good sense from a functional perspective (Glimcher, 2003). Furthermore, it is well known that the nervous system is able to predict expected payoffs (Schultz et al., 2000) and that activities in movement-related brain regions are modulated by those estimates (Coe et al., 2002; Hoshi et al., 2000; Platt and Glimcher, 1999; Roesch and Olson, 2003; Schultz et al., 2000). The present findings provide further support for the hypothesis that the options for a

behavioral decision are expressed in terms of potential actions, and the competition between them plays out in large part within the corresponding motor-related regions.

Experimental Procedures

Two male monkeys (*Macaca mulatta*, Y and Z) performed instructed-delay reaching tasks by moving a handle in the horizontal plane out of sight at waist level to control a cursor on a monitor screen at eye level 48 cm away (handle position sampled at 50 Hz; GP 9, Science Accessories). Eye movements were unconstrained and measured using an infrared oculometer (100 Hz; Dr. Bouis; Karlsruhe, Germany).

In the two-target task (Figure 1A), monkeys began each trial by moving the cursor into a central green circle (1.5 cm radius) for 500 ms (center-hold time [CHT]). Next, a red and a blue cue circle (2 cm radius) appeared at two of eight possible target locations around a circle of 8 cm radius for 1000 ms (spatial-cue [SC]). The two cues were usually in opposite directions from the center. In some sessions, they were 90° apart. The cues then disappeared for 500–1500 ms (memory [MEM]). Next, the central circle changed color to red or blue for 1500–2500 ms (color-cue [CC]). This nonspatial cue signaled which of the two memorized color-coded spatial cue locations was the selected target. The CC period ended when the central circle disappeared and green circles (2 cm radius) appeared at all eight peripheral locations. At this GO signal, the monkeys moved the cursor from the central circle to the selected target. Reaction time (RT) was the time between GO signal onset and the onset of movement. Movement time (MT) was defined between onset and end of movement. If the monkey held the cursor in the correct target for 1000 ms (target-hold time [THT]), it received a juice reward. Trials were presented in a randomized-block sequence balanced for all combinations of location-color conjunctions, color cues, and selected target locations. Trials in which an error occurred were shuffled back randomly into the remaining block sequence.

There were two control task variants. In a one-target task (Figure 1B), only one spatial cue appeared in SC, whose color always matched that of the central cue during CC. Thus, one movement direction was specified with full certainty from the onset of the SC period. In the match-to-sample (MS) task (Figure 1C), the order of presentation of cues was reversed. The central color changed first (500–1500 ms), and then two spatial cues appeared (2500–3500 ms). The initial color cue in the MS task was uninformative about movement direction but was behaviorally salient and essential to select the correct target between the two subsequent spatial cues. There was no MEM period in the MS task.

See the Supplemental Data for details of neuronal recording and histology.

Directional Tuning

For each neuron, the mean discharge rate (including partial spike intervals) was calculated for each epoch of each trial (Georgopoulos et al., 1982, 1988; Kalaska et al., 1989; Sergio and Kalaska, 2003). A mean directional tuning curve was calculated for each epoch by averaging the activity from all trials with a selected target at each of the eight directions. The preferred direction (PD) was calculated using trigonometric moments. Each curve was tested for unimodal tuning by a nonparametric bootstrap test (Georgopoulos et al., 1988; 1000 repetitions, $p < 0.01$). If it failed this test, it was then tested for bimodal tuning by doubling the angles, repeating the bootstrap test and PD calculation, and dividing the resulting PD angle by 2. If the bootstrap test now passed significance, the PD defined the major axis of a bimodal tuning function. Response curves that failed the criteria for both unimodal and bimodal tuning were considered untuned.

Cells were grouped into four classes. A potential-response (PR) cell was bimodally tuned during the SC and/or MEM period of the two-target task, but not during the SC period of the one-target task. A selected-response (SR) cell was untuned during the SC period of the two-target task, but unimodally tuned during the subsequent CC period and during the SC period of the one-target task. A build-up (BU) cell was untuned during the SC periods, but unimodally tuned during the CC periods of both 1- and two-target tasks. A movement (M) cell was unimodally tuned during the RT, MT, or THT periods of both tasks, but failed the criteria for PR, SR, and BU cells during the delay periods. Unclassified neurons failed all of these criteria. The percentage of neurons in different classes refers to the final sample of recorded cells. In the richest cortical regions, nearly every isolatable cell was task related and recorded, so the sample is not grossly biased.

Latency

The time at which a cell signaled the location of the selected target in the two-target task was determined from the difference in mean CC-period activity of trials in which the selected target was in the cell's PD or the opposite direction (OD) (Sato and Schall, 2003). The mean spike rates (using partial spike intervals) of PD trials and OD trials were collected in 1 ms bins aligned at CC onset. Binned rates were square-root transformed to make their variance independent of the mean (Moran and Schwartz, 1999). The time of target selection was defined as the time at which the difference between the spike trains exceeded the mean + 2 × SD of the difference in background activity during the 500 ms prior to CC onset, provided that the difference remained above this criterion for at least 50 ms and eventually exceeded the mean + 5 × SD of baseline. A similar procedure identified the time at which a cell signaled the location of spatial cues in the two-target task, using the difference in binned SC-period activity between trials in which a spatial cue appeared near the cell's PD or orthogonal to the PD.

Population Analyses

Population histograms were generated for each task. Each cell's PD was defined using data from the RT epoch of the one-target task. Only cells that were directionally tuned in that epoch were included. Population data were also displayed as 2D color contour plots, with each row representing the location of the selected target with respect to each cell's PD (interpolated to angles of 11.25°), and each column representing time with respect to SC, CC, and GO signal onset.

Population response latencies to various task events were calculated by a subtraction method like that described above for single cells. Since population histograms are smoother than single-cell histograms, the threshold was set at mean + 1.5 × SD of baseline activity, and the minimum duration was set at 10 ms.

Supplemental Data

Supplemental Data and Supplemental Figures for this article can be found online at http://www.neuron.org/cgi/content/full/45/5/801/DC1/.

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