

# Direction of action is represented in the ventral premotor cortex

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**The ventral premotor area (PMv) is a major source of input to the primary motor cortex (M1). To examine the potential hierarchical processing between these motor areas, we recorded the activity of PMv neurons in a monkey trained to perform wrist movements in different directions with the wrist in three different postures. The task dissociated three major variables of wrist movement: muscle activity, direction of joint movement and direction of movement in space. Many PMv neurons were directionally tuned. Nearly all of these neurons (61/65, 94%) were 'extrinsic-like'; they seemed to encode the direction of movement in space independent of forearm posture. These results are strikingly different from results from M1 of the same animal, and suggest that intracortical processing between PMv and M1 may contribute to a sensorimotor transformation between extrinsic and intrinsic coordinate frames.**

To generate a goal-directed movement, the brain must translate the location of a target, specified in an external coordinate frame, into a set of muscle activation patterns, specified in an intrinsic coordinate frame. Insight into the sensorimotor transformations involved in this process<sup>1,2</sup> and how these transformations are implemented in the central nervous system can be gained by examining the reference frames of neurons in different sensory and motor areas of the brain<sup>3</sup>. We developed a protocol that dissociates three different coordinate frames related to wrist movements: extrinsic (related to the direction of movement in space), muscle (related to the activity of individual or groups of muscles) and joint (related to the angle of the wrist joint). In a previous study, we used this protocol to examine neuron activity in M1 (ref. 4). The protocol enabled us to distinguish two types of M1 neurons, one that seemed to represent the direction of movement in space ('extrinsic-like') and one that seemed to represent muscle activity ('muscle-like').

Here we used the same protocol to examine neural activity in the PMv. The PMv is located rostral and lateral to the forelimb region of M1 and is densely interconnected with it<sup>5,6</sup>. The PMv also has strong interconnections with regions of posterior parietal cortex<sup>7-9</sup> and is the only premotor area interconnected with area 46 in prefrontal cortex<sup>10</sup>. Neurons in the PMv receive visual and somatosensory inputs<sup>11-15</sup> and are active during the preparation for and execution of visually guided movements<sup>11,16-19</sup>. Lesions involving the PMv disrupt movements directed toward visual targets<sup>20</sup>. These and other observations suggest that the PMv is an important member of the cortical network for directing limb movement in space. Thus, we compared the reference frames of neurons in the PMv with those of M1 to gain insight into the coordinate transformations that may occur between these areas. To facilitate this comparison, we recorded PMv neurons in the same animal that was used to study M1.

In contrast to our results for M1, we found that most directionally tuned PMv neurons encoded movement in an extrinsic-like coordinate frame and were not influenced by changes in

forearm posture. Our findings are consistent with a hierarchical relationship between PMv and M1. Specifically, intracortical processing between PMv and M1 might transform target location in an extrinsic reference frame into a movement goal in an intrinsic, limb-centered reference frame.

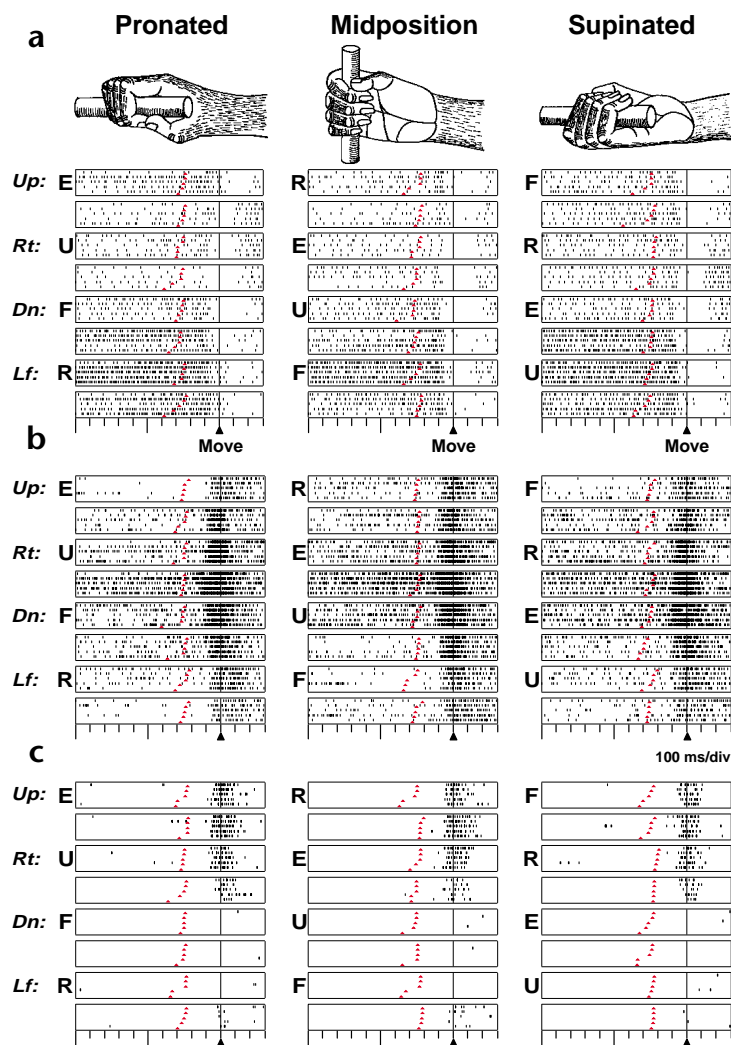
## RESULTS

We recorded the activity of PMv neurons while a monkey performed wrist movements in eight different directions. These movements required different combinations of flexion-extension and radial-ulnar deviation, and were made with the wrist in three separate postures: pronated, supinated and midway between pronation and supination (Fig. 1, top). We found 117 neurons in the PMv that displayed marked changes in activity during the instruction and/or execution periods of this task. Overall, changes in activity during the instruction period were more frequently found in PMv (60/117 neurons) than in M1 (33/125 neurons;  $p < 0.001$ ,  $\chi^2$  test).

Among the task-related neurons in the PMv, 65 neurons were directionally tuned in all three wrist postures (Figs. 1 and 2, Table 1). These neurons are the focus of the present report. A few PMv neurons were directionally tuned in one or two postures (12/117). The remaining neurons in the sample (40/117) either were not directionally tuned or were difficult to classify. By comparison, 88 of 125 task-related neurons in M1 were directionally tuned for all three wrist postures<sup>4</sup>.

We found neurons that were directionally tuned for all three postures in a region of the PMv that was located rostral and slightly lateral to the wrist area in M1 (Fig. 3). These neurons were recorded at depths that ranged from 1.50 to 6.00 mm from the cortical surface, but most were recorded at 2-3.5 mm (mean  $\pm$  s.d.,  $2.90 \pm 0.89$  mm,  $n = 47$ ). Most directionally tuned neurons in the PMv (47/65, 72%) were concentrated in a small region near or in the caudal bank of the arcuate sulcus (dotted line in Fig. 3).

Directional tuning was present either during the instruction period ( $n = 6$ , for example, Figs. 1a and 2a), during the execu-



**Fig. 1.** Directionally tuned activity of three neurons in the PMv. Top, monkey right hand gripping the handle of the manipulator in three wrist postures: pronated, midposition (midway between pronation and supination), supinated. Each column shows neuron activity for a single wrist posture. Each row shows neuron activity for a single direction of movement in extrinsic space. The letters in the upper left hand corner of each raster indicate the direction of joint movement. R, radial deviation; E, extension; U, ulnar deviation; F, flexion. Rasters are aligned on movement onset (Move, large black triangles). Small red triangles in the rasters to the left of movement onset indicate the go signal. All three neurons were recorded within the dotted area indicated in Fig. 3. (a) A neuron with extrinsic-like activity during the instruction period only. Stimulation at the recording site evoked no visible movement at an intensity of up to  $40 \mu\text{A}$ . The neuron was activated by cutaneous stimulation of either forearm. (b) A neuron with extrinsic-like activity during both the instruction and execution periods. Stimulation at the recording site evoked no visible movement at an intensity of up to  $40 \mu\text{A}$ . The neuron was activated by passive manipulation of the wrist and elbow joint. (c) A neuron with extrinsic-like activity during the execution period only. Stimulation at the recording site evoked extension of the wrist at a threshold of  $40 \mu\text{A}$ . The neuron was activated by passive manipulation of the wrist and by touching the hairy skin of the upper jaw.

tion period ( $n = 35$ , for example, Figs. 1c and 2c) or during both periods ( $n = 24$ , for example, Figs. 1b and 2b). We determined a preferred direction (direction of maximum activity) in the relevant time window(s) for each directionally tuned neuron in each of the three wrist postures. This enabled us to examine whether the preferred direction and the magnitude of neuron activity were altered by changes in forearm posture.

### Extrinsic-like neurons

Almost all the directionally tuned neurons in the PMv ( $n = 61/65$ , 94%) showed little change in preferred direction when the forearm posture was rotated by  $180^\circ$  from pronated to supinated (Figs. 1 and 2). Thus, we categorized nearly all the directionally tuned neurons in the PMv as extrinsic-like, because they showed a shift in preferred direction of less than  $\pm 35^\circ$  for a  $180^\circ$  rotation of the forearm<sup>4</sup>. Furthermore, the shift in preferred direction was not statistically significant ( $p > 0.3$ ) for almost all these extrinsic-like neurons ( $n = 58/61$ ).

Extrinsic-like patterns of activity were recorded from PMv neurons during both the instruction and execution periods (Figs. 1, 2 and 4; Table 1). Indeed, all six of the PMv neurons with directionally tuned activity only during the instruction period were extrinsic-like (for example, Figs. 1a and 2a). Similarly, 23 of 24 neurons with directionally tuned activity during both periods (for example, Figs. 1b and 2b) and 32 of 35 neurons with directional-

ly tuned activity during the execution period only (for example, Figs. 1c and 2c) were extrinsic-like.

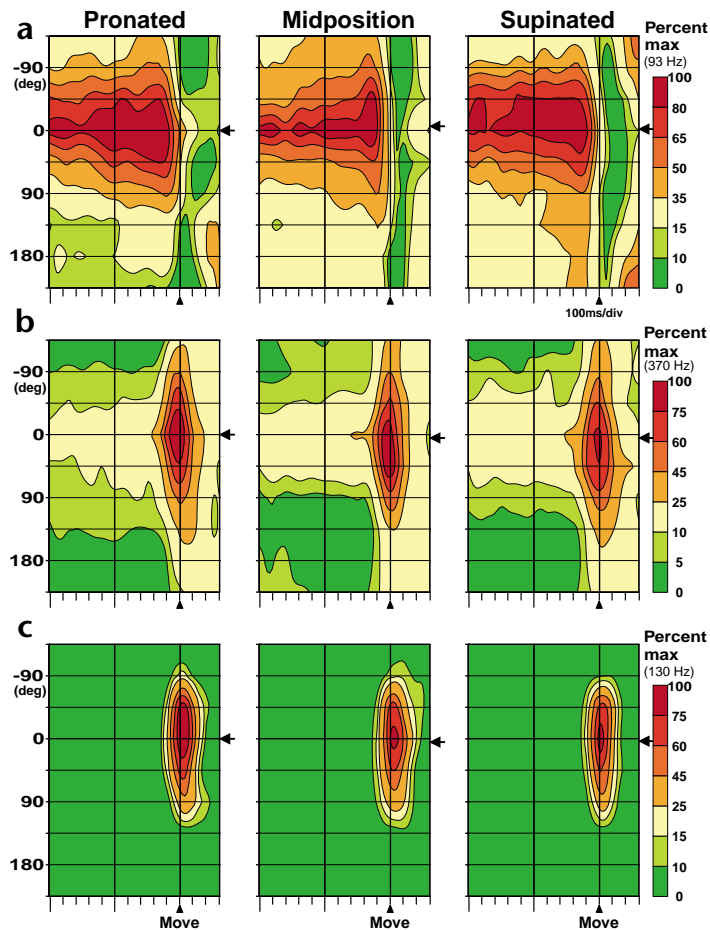
All directions of movement were represented by the preferred directions of different extrinsic-like neurons (Fig. 5a). In general, the preferred direction of a neuron's activity in the instruction period was highly and positively correlated with its preferred direction during the execution period (Fig. 5b). One neuron in the PMv displayed a striking inverse relationship between the preferred directions of activity during the execution and instruction periods (asterisk, Fig. 5b). Taken together, these results indicate that the activity of extrinsic-like neurons in the PMv

reflects the spatial aspects of movement during both the preparatory and execution periods of a movement.

Most extrinsic-like neurons in the PMv (47/61, 77%) displayed no modulation in the magnitude of their activity with changes in posture (Figs. 1, 2 and 4). This result contrasts with our previous observations on the activity of forearm muscles and M1 neurons. Most forearm muscles (17/23 recordings), most muscle-like neurons in M1 (18/27), and a majority of the extrinsic-like neurons in M1 (27/44) exhibited strong modulations in the magnitude of their responses in different postures (Fig. 4). Thus, extrinsic-like neurons in PMv seem to represent motor output in a more abstract form than neurons with extrinsic-like properties in M1.

Extrinsic-like neurons in the PMv exhibited earlier changes in movement-related activity (mean,  $-124.3 \pm 30.6$  ms) than extrinsic-like neurons in M1 (mean,  $-97.0 \pm 15.3$  ms,  $p < 0.0005$ , Mann-Whitney U-test, Fig. 6). This observation provides further support for a hierarchical arrangement of interactions between the PMv and M1. Even within the PMv, there were differences in the timing of movement-related activity between classes of neurons (data not shown). PMv neurons that were task-related during both the instruction and execution periods displayed earlier changes in movement-related activity (mean,  $-140.0 \pm 29.4$  ms before movement) than PMv neurons that were task-related only during the execution period (mean change,  $-114.4 \pm 26.4$  ms,  $p < 0.005$ , Student's *t*-test).

**Fig. 2.** Spatiotemporal maps of extrinsic-like activity in the PMv. Same neurons (a, b, c) as in Fig. 1. These maps were constructed from the average number of spikes in successive 50-ms time bins using Surfer (Golden Software, Golden, Colorado). Ordinate, percentage of maximum activity in a 50-ms time bin for any of the 3 postures. The maps are displayed with the preferred direction of each neuron in the pronated posture normalized to 0°. The maps of activity in the midposition and supinated postures are plotted relative to those in the pronated posture to illustrate the shift in preferred direction. Arrows on the right ordinate of each graph indicate the preferred direction for each posture.



**Intrinsic-like neurons**

Only a few directionally tuned neurons in the PMv (4/65, 6%) had orderly and relatively large (>40°) shifts in preferred direction when the posture of the forearm was rotated 180° clockwise from pronated to supinated (Fig. 4). We consider these neurons to be ‘intrinsic-like’ because their shift in preferred direction paralleled that expected of a neuron related to the wrist joint or that observed for task-related muscles. The relative absence of intrinsic-like neurons in the PMv (6%) contrasts with the substantial population of these neurons in M1 of the same animal (28/88, 32%)<sup>4</sup>.

**DISCUSSION**

The PMv, like M1, contained many neurons that were strongly related to step-tracking movements of the wrist. However, the populations of directionally tuned neurons in the PMv and M1 showed striking differences. Nearly all directionally tuned neurons in the PMv (~94%) were extrinsic-like; they displayed little or no shift in their preferred direction with large changes in forearm posture. Forearm posture also had little influence on the magnitude of the movement-related activity of most PMv neurons (~77%). In contrast, M1 contains a substantial population of directionally tuned neurons that are intrinsic-like (~32%); they display large and systematic shifts in their preferred direction with changes in forearm posture<sup>4</sup>. Furthermore, forearm posture modulates the movement-related activity of most extrinsic-like neurons in M1 (~61%). Another salient difference between the two motor areas was that on average, the movement-related activity of extrinsic-like neurons in the PMv occurred earlier than the corresponding activity in M1. All of these observations are consistent with the proposal that the PMv is involved in the spatial guidance of limb movements and that it functions at an earlier stage of sensorimotor processing than M1.

What aspects of movement are represented by the extrinsic-like activity of PMv neurons? At this point, there is no definitive answer to this question. Our task dissociated movement parameters related to an intrinsic coordinate frame from those related to an extrinsic frame. However, it was not designed to

dissociate several extrinsic factors, such as the direction of limb movement in space, the direction of movement of the object acted upon (the cursor), and the goal or final result of the movement. As a consequence, the extrinsic-like activity of neurons in the PMv might represent any one or more of these variables. Indeed, the apparently homogeneous population of extrinsic-like neurons in the PMv might be composed of multiple subpopulations, each encoding a distinct extrinsic-like feature of movement (for example, see ref. 21). We are currently testing this possibility.

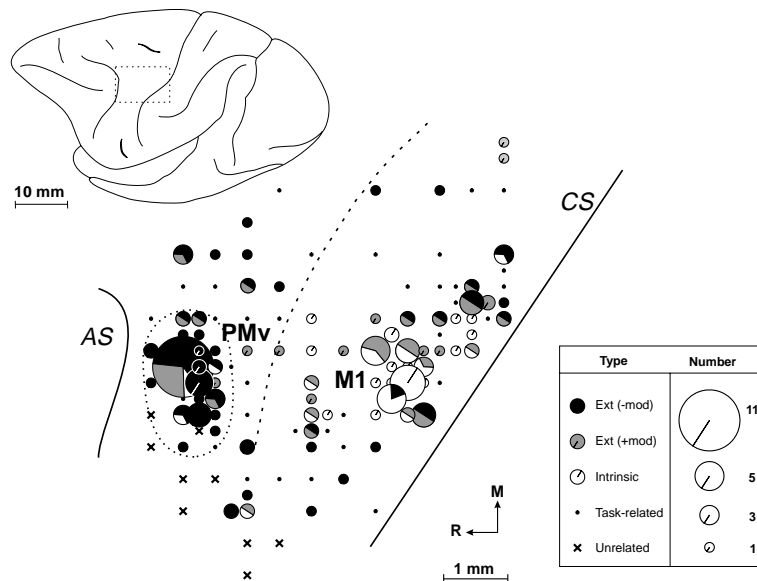
Regardless of the extrinsic-like parameters encoded by the activity of PMv neurons, our experiments clearly demonstrated that the motor representation in the PMv is independent of joint- or muscle-related details of movement. Our findings are consistent with a previous speculation that the activity of PMv neurons signals the goal of a movement, regardless of how the goal is accomplished<sup>22</sup>. Indeed, our results have provided an unambiguous demonstration of the independence of PMv activity from intrinsic parameters of movement.

Previously, researchers described two types of PMv neurons with unique responses to visual stimuli—‘canonical’ and ‘mirror’ neurons (see refs. 23, 24 for review). Canonical neurons respond to the visual presentation of three-dimensional objects of different sizes and shapes. The motor responses of these neurons are limited to specific goal-directed actions toward these objects. Canonical neurons were largely found in the portion of the PMv that is buried in the bank of the arcuate sulcus. Mirror neurons are active when a monkey executes a specific action and when the monkey watches someone else perform a similar action<sup>25</sup>.

**Table 1. Directionally tuned neurons and task period.**

	Extrinsic	Intrinsic	Total neurons
Instruction period	6	0	6
Execution period	32	3	35
Instruction + execution	23	1	24

**Fig. 3.** Distribution of neuron types in the PMv and M1. Top left, lateral view of the left hemisphere. The dashed rectangle indicates the region of neuron recording (enlarged in the center of the diagram). Center, map of recording sites. Each circle is centered on the surface location of an electrode penetration. The diameter of the circle is proportional to the number of neurons recorded in each track. Ext (-mod), extrinsic-like neurons without modulation of activity by forearm posture; ext (+mod), extrinsic-like neurons with modulation of activity by forearm posture; intrinsic, intrinsic-like neurons (that is, those with a shift in preferred direction greater than 40°); task-related, task-related neurons that were non-directional or unclassified; unrelated, non-task-related neurons. Dashed line, estimated border between M1 and the PMv; dotted line, main focus of directionally tuned activity in the PMv. CS, central sulcus; AS, arcuate sulcus.



These neurons were largely found in the portion of the PMv that is on the cortical surface caudal to the arcuate sulcus. The presence of mirror and canonical neurons, along with the extrinsic coding that we found, suggests that the PMv may contain a spatial representation of actions.

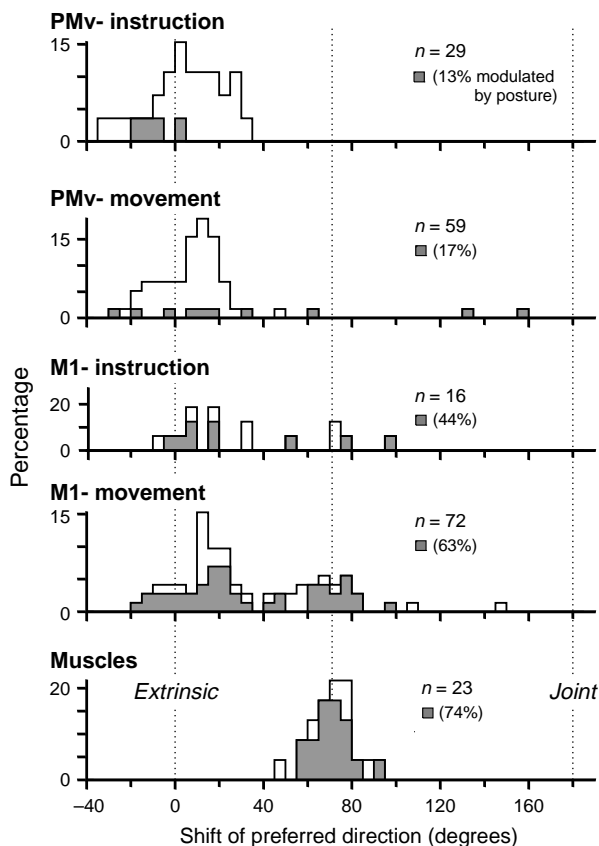
Anatomical studies of the PMv have demonstrated that this premotor area has strong interconnections with regions of posterior parietal cortex and dense projections to primary motor cortex<sup>7-10,26</sup>. Based on these connections, we suggest that the extrinsic-like activity of PMv neurons may be involved in the transformation of target location in a visual frame of reference into the direction of action needed to acquire the target in a motor frame of reference. This proposal is similar to the suggestion that PMv neurons translate the visual features of an object

into a potential motor action<sup>27</sup>. Many studies of PMv neurons have emphasized their role in the organization of grasping movements and the manipulation of objects. Our experiments indicate that PMv function is not limited to these types of movement, but includes a broader aspect of skeletomotor control.

There has been considerable interest in using signals from the central nervous system to drive prosthetic devices and/or robotic arms<sup>28</sup> (S. I. Helms-Tillery *et al. Soc. Neurosci. Abstr.* 26, 458.2, 2000). In most instances, investigators have found that signals from single neurons do not provide enough information for this purpose. Therefore, they have used populations of neurons to derive the appropriate control signals. Our results indicate that single neurons in the PMv appear to encode a 'higher-order' representation of action. If the PMv contains a similar set of neurons related to arm movements, then single neurons in this cortical area might be an especially good source of signals for the neural control of prostheses.

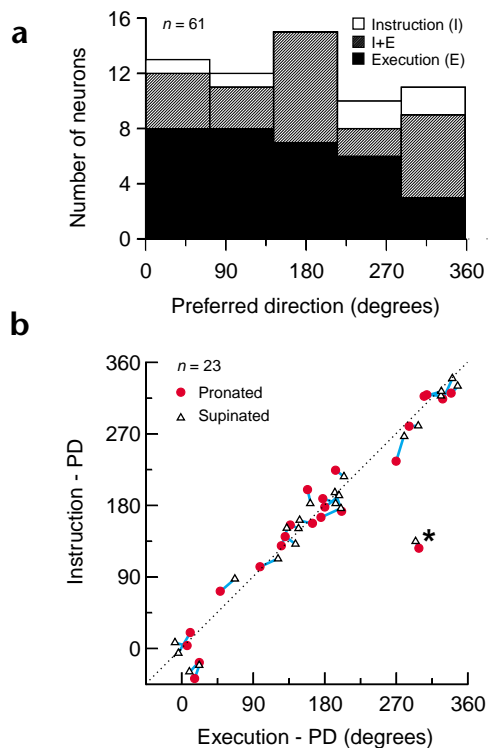
**METHODS**

**Animal and task.** Our experiment was performed on a male rhesus monkey (*Macaca mulatta*, 15.0 kg). We recently reported the results of neuron recordings in M1 of this animal when it performed the same task as that used in the present study<sup>4</sup>. All experimental procedures were conducted according to National Institutes of Health guidelines and were



**Fig. 4.** Preferred directions of neurons and forearm muscles. Histograms display the shifts in preferred direction for a 180° clockwise rotation of wrist posture from pronated to supinated (see text for details). Clockwise shifts are positive. The dotted line labeled 'intrinsic' indicates an ideal extrinsic-like preferred direction that does not shift with changes in wrist posture. The dotted line labeled 'joint' indicates an ideal preferred direction related to the wrist joint that shifts 180° with a change in wrist posture from pronated to supinated. The unlabeled dotted line in the middle indicates the average shift (71.1°) of activity in seven task-related muscles<sup>4</sup>. The shaded areas indicate neurons or muscles with peak activity that was modulated (>30%) by changes in wrist posture. PMv-instruction, shift in preferred direction for PMv neurons with instruction period activity. PMv-movement, shift in preferred direction for PMv neurons with execution period activity. M1-instruction, shift in preferred direction for M1 neurons with instruction period activity. M1-movement, shift in preferred direction for M1 neurons with execution period activity. Muscles, shift in preferred direction for task-related muscles (23 recordings from 7 forearm muscles)<sup>4</sup>.





**Fig. 5.** Extrinsic-like neurons in the PMv. (a) Distribution of preferred directions. The shading indicates the task period with directionally tuned activity. Twenty-three neurons displayed directionally tuned activity during both the instruction and the execution periods (gray). Six neurons displayed directionally tuned activity only during the instruction period (white). Thirty-two neurons displayed directionally tuned activity only during the execution period (black). Abscissa, 0°, up; 90°, right; 180°, down; 270°, left. (b) Relationship between preferred directions during the execution and instruction periods. Each neuron in the PMv that displayed directionally tuned activity during both task periods is plotted in this graph (23 neurons). A neuron with the same preferred direction (PD) during both periods falls on the dotted line ( $y = x$ ). The asterisk marks a neuron whose preferred direction during the execution period was opposite to its preferred direction during the instruction period.

approved by the institutional animal care and use committees of the Syracuse VA Medical Center, the SUNY Upstate Medical University and the University of Pittsburgh Medical School.

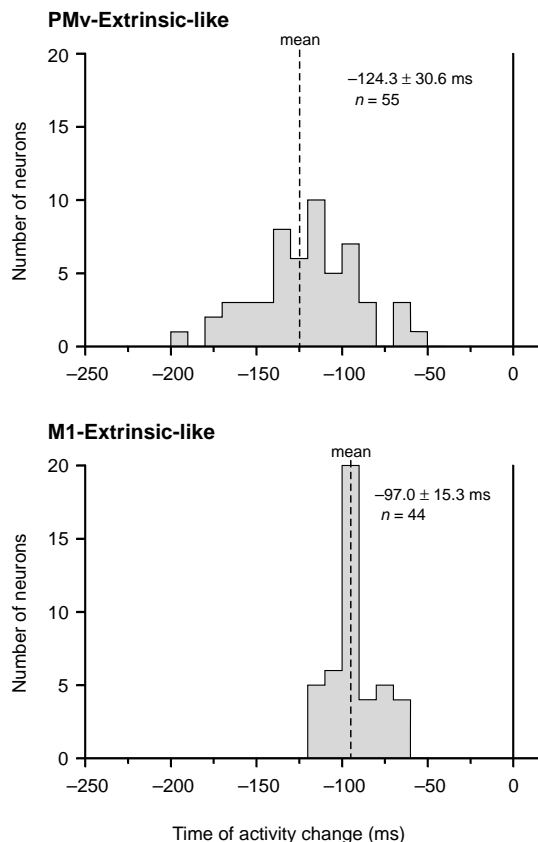
The monkey was trained to make rapid step-tracking movements of the right wrist for a liquid reward. The animal sat in a primate chair with its forearm supported and grasped the handle of a lightweight, low-friction manipulandum (see Fig. 1 in ref. 29). The device rotated about the two axes of wrist joint motion: flexion–extension and radial–ulnar deviation. Potentiometers at each axis measured rotation in the two planes of joint motion. The monkey faced a large computer screen that displayed a ‘cursor’ and a ‘target.’ The cursor was a small filled circle that moved in proportion to the animal’s wrist movements. The target was a larger open circle whose inside diameter equaled 8° of wrist movement. At the start of each trial, the target was placed in the center of the screen. The monkey began the task by placing the cursor in the target. After a variable ‘hold’ period (0.75–1.5 s), a second target appeared at a peripheral location on the screen. Following a variable ‘instruction’ period (1–3 s), the central target was extinguished. This served as a ‘go’ signal that told the animal to move from the central to the peripheral target. The animal was allowed 200 ms to complete the initial trajectory of the movement. Target locations required a 20° change in wrist angle.

We required the monkey to move to 8 peripheral target locations that were evenly spaced at intervals 45° apart and required 8 different combinations of wrist flexion–extension and radial–ulnar deviation. The monkey performed the task with the forearm in each of three different postures: pronated, supinated and midway between pronation and supination. The change in forearm posture resulted in a dissociation of the direction of joint movement from the direction of movement in space. For instance, when the forearm was rotated 180° clockwise from pronated to supinated, a coordinate frame linked to the wrist joint also shifted by 180° clock-

wise. On the other hand, an extrinsic coordinate frame remained stable regardless of forearm posture. Furthermore, we previously demonstrated that the preferred directions of muscle activity shifted an intermediate amount (mean, 71.1°; range, 46–90°) for a 180° clockwise rotation of the forearm<sup>4</sup>. Thus, a key feature of the task is that it exclusively dissociates three major variables of wrist movement: direction of movement in space, direction of movement at the wrist joint and activity of forearm muscles. The monkey was trained for more than eight years on this task, and as a consequence, his performance was stable.

**Surgery and recording.** We used conventional techniques for extracellular recording of single neuron activity in the PMv. A device for head restraint and a recording chamber were implanted using aseptic techniques and inhalation anesthesia (3% isoflurane + 1% N<sub>2</sub>O). The recording chamber was large enough to provide access to M1 and PMv. When the animal had recovered from surgery, we used glass-coated Elgiloy electrodes (0.9–1.5 MΩ) to record neuron activity. For each task-related neuron, we recorded activity while the animal made 5 to 10 movements to each tar-

**Fig. 6.** Timing contrast between extrinsic-like neurons in the PMv and M1. The time of activity change in relation to movement onset is plotted for each PMv and M1 neuron with directionally tuned activity during the execution period (PMv,  $n = 55$ ; M1,  $n = 44$ ). Negative time values indicate a change in activity before movement onset. The mean time of change for movement-related activity in the PMv is significantly earlier than that in M1 ( $p < 0.0005$ , Mann–Whitney U-test).



get location. The eight target locations were presented in a randomized block design. Once a complete set of trials was collected for one posture, complete sets of trials were collected for the other two postures. Next, while the animal was relaxed, we examined the peripheral receptive fields of recorded neurons. We used passive movement, palpation or brushing of the fingers, forearm, upperarm, shoulder, chest, back, neck and face on both sides of the body to search for somatosensory afferent input. For neurons with a receptive field on the hand or forearm, we mapped the receptive field with the wrist in each of the three postures. Because many PMv neurons responded to visual stimuli, we covered the animal's eyes when mapping somatosensory responses. We also noted visual responses to directional movements of the examiner's hand in front of the animal or approach of the examiner's hand toward the animal's body.

We identified the forearm region of PMv using the somatosensory responses of recorded neurons and the effects of microstimulation (pulse duration, 0.2 ms, 333 Hz for either 60 or 90 ms). Most neurons (83/120) in the forearm region of PMv were activated by passive movements of the wrist and/or fingers and by palpation of forearm muscles or light brushing on the forearm. Some of these neurons (30/120) also had large receptive fields that included more proximal and axial body parts (upperarm, shoulder, chest, back, neck and face). Microstimulation in the PMv at  $\leq 35$ – $40$   $\mu$ A produced an observable movement at most (84/120) recording sites. PMv was distinguished from M1 because the threshold for movement was generally  $\geq 15$   $\mu$ A in the PMv (79/84) and generally  $\leq 15$   $\mu$ A in M1 (note 22 in ref. 4). Other studies have shown that an increase in the microstimulation threshold corresponds closely to the cytoarchitectonic border between the areas<sup>30–32</sup>.

Before neuron recording, we examined the activity of 15 forearm, 5 upperarm, and 7 shoulder muscles while the monkey performed the task. Electromyograms (EMGs) were recorded using pairs of single-stranded stainless steel wires placed transcutaneously into each muscle. We stimulated through each intramuscular electrode to confirm its location. Only four wrist muscles and three finger muscles displayed phasic agonist bursts with amplitudes that varied for different directions of movement (for details, see ref. 4, 33).

**Data analysis.** One hundred and twenty neurons in the PMv were considered task-related, because they displayed a statistically significant change in activity (ANOVA;  $p < 0.05$ ) during either the instruction or execution period (defined below). Three of these neurons were considered to be weakly related because they displayed modulations in activity that were less than 20 Hz during the instruction period or less than 50 Hz during the execution period. These neurons were eliminated from further consideration.

We used a bootstrapping method ( $p < 0.01$ )<sup>34</sup> to determine whether a task-related neuron was directionally tuned. Next, we determined the preferred direction (direction of maximum activity)<sup>35</sup> of directionally tuned neurons in two time windows. The preferred direction for the instruction period was measured from  $-300$  to  $0$  ms relative to the go signal; the preferred direction for the execution period was measured from  $-100$  to  $0$  ms relative to the onset of movement. This analysis was performed for each of the three wrist postures. For muscle activity, the preferred direction was calculated in a time window of  $\pm 25$  ms relative to movement onset<sup>4</sup>.

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