



The role of primary motor cortex in goal-directed movements: insights from neurophysiological studies on non-human primates

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Neurophysiological studies on non-human primates have provided a large body of information on the response patterns of neurons in primary motor cortex during volitional motor tasks. Rather than finding a single simple pattern of activity in primary motor cortex neurons, these studies illustrate that neural activity in this area reflects many different types of information, including spatial goals, hand motion, joint motion, force output and electromyographic activity. This richness in the response characteristics of neurons makes estimates of any single variable on motor performance from population signals imprecise and prone to errors. It initially seems puzzling that so many different types of information are represented in primary motor cortex. However, such richness in neural responses reflects its important role in converting high-level behavioral goals generated in other cortical regions into complex spatiotemporal patterns to control not only α -motoneuron activity but also other features of spinal processing.

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Abbreviations

MI primary motor cortex

Introduction

There is little disagreement that primary motor cortex (MI) plays a pivotal role in volitional motor control, such as reaching and grasping objects of interest in the environment. MI receives considerable converging input from many cortical and subcortical regions and it provides the largest contribution to the descending corticospinal tract, with some of these neurons synapsing directly onto α -motoneurons [1]. Many recent reviews have discussed the role of MI in motor control, learning and skill acquisition [2,3,4,5,6].

One approach for interpreting brain function is to assess the response characteristics of neurons in awake, behaving animals. These techniques, first developed by H

Jasper and applied by E Evarts to the MI of non-human primates [7], provide an important avenue to assess what type of information is represented in the activity patterns of individual neurons. A large body of literature has been generated on the activity of neurons in MI during behavior, but the interpretation of these responses and the associated function of MI remains strongly debated. Here, I discuss aspects of this debate and how it relates to experimental challenges of relating neural activity to specific features of motor performance, as well as the complex role played by MI in controlling motor function.

Population vectors and correlates of hand motion

Neurophysiological studies conducted in the 70s focused largely on the relationship between the activity of individual neurons in MI and the motor actions at a single-joint. The studies by Georgopoulos and co-workers [8,9] in the early 80s emphasized the utility of exploring whole-limb reaching movements and examining how the activity across a population of neurons was related to motor behavior. They introduced the population vector method to estimate the relationship between MI activity and the direction of hand motion. Each neuron voted for a preferred direction of movement, the direction at which it was maximally active. The number of votes cast by each neuron corresponded to its discharge rate for a given movement. These individual neural vectors were summed to create a population vector. The initial observation was that the population vector tended to point in the direction of hand motion [9], with subsequent work suggesting that population vector length reflected movement speed [10]. Over the past twenty years, a large battery of studies have shown how population vectors could estimate the direction of hand motion.

So what is the significance of a population vector pointing in the direction of movement? It could mean that neurons in MI specify global information on motor performance related to the direction of hand motion [8]. Alternatively, theoretical studies suggest that neural activity reflecting myriad coordinate frames could generate population vectors that point in the direction of movement if three conditions are met: first, neural tuning is symmetric, second, there is a uniform distribution of preferred directions across the cell sample and third, there is no coupling between the preferred direction of a neuron and how much it modulates its activity during movement [11,12,13]. Satisfying these three conditions does not necessarily mean that neurons are coding hand motion. This point was illustrated in Todorov [13] where several

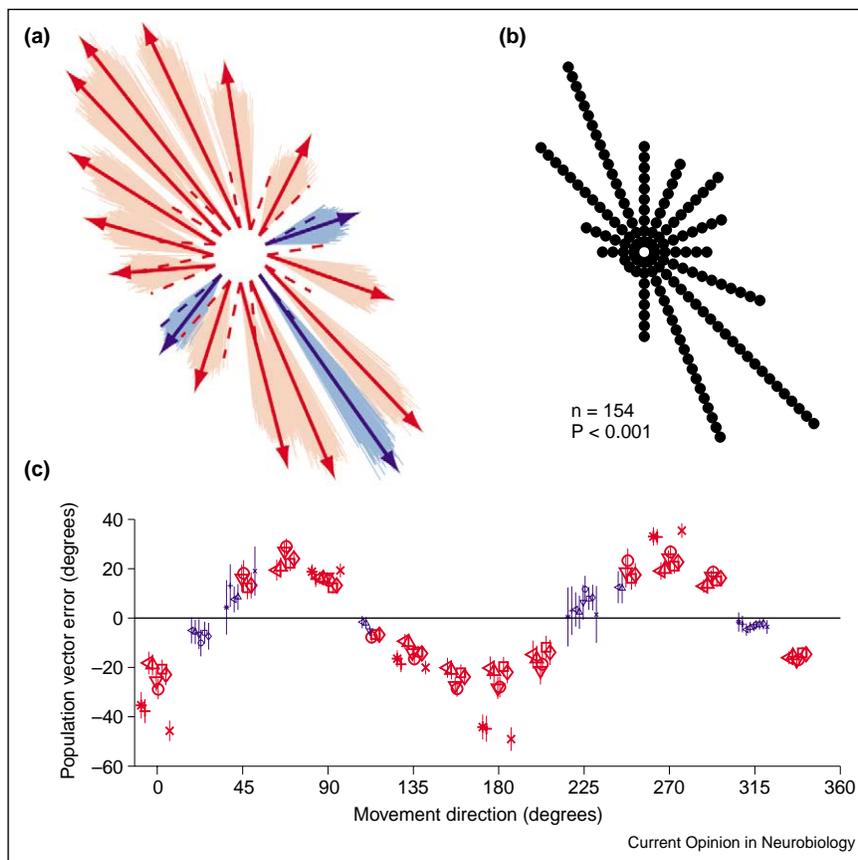
previous observations on correlates of hand motion using population vectors were replicated by a model with a population of neurons coding muscle activities. A correlate of mental rotation based on population vectors has also been replicated using a relatively simple model of cortical processing [14].

Recent work on monkeys making limb movements with the arm in the horizontal plane found that population vectors based on MI activity do not always predict the

direction of hand motion [15]. Population vectors are skewed towards one of two directions: movements away from the body and to the left, or towards the body and to the right (Figure 1a). Population vector length varies substantially across movement directions even though movements are all of similar magnitude and have similar peak hand velocities.

The method of constructing population vectors has little effect on the results [16]. Figure 1b illustrates systematic

Figure 1



Differences between population vectors and the direction of hand motion. Analysis based on neurophysiological data from Scott *et al.* [15]. Neural data from one additional monkey has also been included in this analysis. Data in all panels is formed on the basis of neural activity in MI during the reaction time period and hand motion is formed on the basis of the initial 100 ms of movement. (a) Comparison between the direction of hand motion and the population vectors using technique 8 from Georgopoulos *et al.* [85]. All other procedures are described in Scott *et al.* [15]. Movement directions (dashed lines) are attached to the base of each respective population vector. Red arrows denote a significant difference between the direction of the population vector and the direction of hand motion. Blue denotes no difference between the direction of the vector and hand motion, observed for three of the movement directions. Under each population vector is the dispersion of population vectors formed on the basis of a random re-sampling of the cell population with replacement. (b) Systematic errors between the direction of hand motion and the population vectors using nine different techniques to compute population vectors. Neurons were included in each technique if their activity was significantly related to the direction of movement ($p < 0.05$; raw discharge used plate method [86], cosine and von Mises [a normal distribution for circular statistics] tuning functions tested for significant model fit). Symbols \times , $+$, $*$, \circ , \square , and \diamond denote weighting functions 2, 4, 6, 8, 10 and 12, respectively, from Georgopoulos *et al.* [85]. Symbols ∇ , \triangle , \triangleleft denote weighting functions 8, 10 and 12, respectively, from Georgopoulos *et al.* [85], but using von Mises tuning functions rather than cosine functions. Larger bold icons reflect significant errors between the direction of hand motion and the population vector, whereas small icons reflect no significant error. (c) Distribution of preferred directions for neurons on the basis of the plate method. Each dot denotes the directional tuning of an individual neuron grouped into 22.5° bins. Distribution of preferred directions was not uniformly distributed as compared to a bimodal distribution (Rayleigh test, $p < 0.001$). There are two large clusters of neurons in the upper left and lower right quadrant. There are also a greater number of neurons in the upper right as compared to the lower left quadrant. As a result, population vector methods in which the baseline activity is not subtracted (odd numbered functions in [85]) create systematic errors as large as 180° (i.e. population vectors point to the upper right for limb movements to the lower left quadrant).

errors in predicting the direction of hand motion for several methods in which some form of baseline subtraction is performed. Techniques in which the baseline activity is not subtracted create systematic errors as large as 180°. A majority of movement directions could not be predicted by population vectors constructed using any of the 18 different techniques examined, including six techniques based on the raw discharge patterns of neurons.

The key reason why population vectors fail to predict movement direction in the study by Scott *et al.* [15], is that the distribution of preferred directions of neurons is not uniform [17,18]. Neurons tend to have preferred directions either away and to the left or towards and to the right (Figure 1c). This bias in the distribution of preferred directions appears to be at least partially due to the mechanical anisotropy of the limb: greater mechanical power is required to initiate limb movements in these two directions, as compared to movements in the other two Cartesian quadrants [19]. The bias also reflects that reaching movements are generated using only two degrees-of-freedom involving shoulder flexion/extension and elbow flexion/extension [20]. Scott and Kalaska [18] illustrated that the distribution of preferred directions becomes more skewed when limb motion is largely in the horizontal plane, as compared to when reaching movements involve at least four degrees-of-freedom, including shoulder flexion/extension, abduction/adduction and internal/external rotation, as well as elbow flexion/extension.

The relationship between cell activity and motor performance

The fact that the mechanics of the limb influence the activity of neurons in MI is certainly consistent with studies that illustrate that many neurons in this region are sensitive to force output [21–23] and correlate with proximal-limb electromyographic (EMG) activity [24,25]. Several mathematical models illustrate how neurons coding either joint kinematics [26] or muscle activities [13] can predict several key properties of neural activity in MI. Yet cells in MI do not appear to reflect any single parameter. Perhaps the most consistent feature of MI activity is the incredible diversity of information that appears to be conveyed in the discharge pattern of individual neurons. Some neurons are strongly sensitive to changes in limb posture or position, whereas others only reflect the global goal of the task, to move in some spatial direction [18,27,28]. Some neurons are sensitive to changes in muscle force, whereas the activity of others is not [21,22]. Some neurons receive strong sensory input, whereas others do not [18]. Some neurons respond to contralateral, ipsilateral or bilateral movements [29,30]. Some neurons even reflect sensory signals used to guide action [31].

It is not that a neuron in MI simply responds only to force, or only to joint kinematics or only to target location, as is

often artificially assumed when statistical methods are used to categorize neurons. Rather, the activity of a given neuron may reflect several of these sensorimotor attributes each with different temporal contributions to cell discharge [32,33]. Furthermore, different parameters are almost certainly not randomly represented across the cell population. If they were random, neural activity would not be unimodally tuned (as is usually observed) and would include multiple peaks each reflecting tuning functions associated with each parameter. Changes in cell activity related to viscous loads applied during reaching tend to occur only along the neurons' preferred direction of movement, suggesting a link between the cells' global tuning function and its specific sensitivity to load [21]. A similar coupling is observed between a cell's tuning function and its response to novel visuomotor transformations [34*].

One solution is to estimate how each different type of variable quantitatively contributes to the discharge pattern of a cell during natural behavior. In theory, this seems plausible but there are substantial hurdles to this approach. First, different variables such as hand and joint motion, and even different joint angles, are inter-correlated during movement [18,35] making it difficult to dissociate these variables experimentally. Second, intrinsic variables such as joint motion and torque are difficult to measure experimentally, and even more challenging to manipulate systematically for anything beyond single-joint movements. Recent robotic technology only now allows two-joint planar arm movements to be sensed and systematically modified [20]. Third, whereas neurons can sometimes show consistent patterns across tasks, such as single- versus multi-joint viscous or bias loads [21,36], neural discharge patterns can show abrupt changes across behavioral contexts [22,37]. Finally, the acquisition of new skills can actually influence the directional tuning properties of neurons [34*,38,39].

Alternative interpretations for correlations with multiple variables: parallel versus serial representations

Why are there so many different variables reflected in the discharge pattern of neurons in MI? This appears to be a troubling problem within the framework of sensorimotor transformations [40,41]. This framework is motivated by the fact that goal-directed reaching movements require the brain to convert spatial information on target location initially defined in retinal coordinates into patterns of proximal-arm muscle activity. The expectation is that there must be some and perhaps several intermediary coordinate frames used by the brain to plan and guide movement, including representations of spatial target direction, hand trajectory, joint angles, joint torques and ultimately muscle activity. Some of this sensorimotor conversion occurs in regions such as the posterior parietal cortex [42*,43] and dorsal premotor cortex [44,45**,46,47],

which results in neural signals reflecting relatively high-level representations of the intentions of motor action. As correlates of so many parameters are found in the discharge pattern of neurons in the MI, it would suggest that this cortical region contributes to many different motor representations.

On the other hand, the richness in the response characteristics of MI neurons is less surprising if one steps away from the idea of sensorimotor transformations and explicit coordinate frames, and simply asks what kind of information is required to control the activity of the spinal cord and for MI to interact with other brain regions. Descending signals must control more than α -motoneuron activity [48,49]. Gamma-motoneurons, which innervate intrafusal fibres in muscle spindles, represent a substantial proportion of a muscle's motoneuron pool [50] and, in some cases, may even be present in equal numbers to α -motoneurons. Gamma-motoneuron activity is modulated on the basis of behavioral context [51], although there is limited information on their patterns of activity during goal-directed movements, what we have is inferred from muscle spindle afferent activity [52–54]. Descending signals are also important for coordinating posture with movement [55,56] and modulating spinal reflexes [57,58]. Neural activity in MI related to these features of subcortical processing may not be that sensitive to changes in force output. Therefore, some neurons in MI reflecting only movement kinematics may be parallel to, and not hierarchically above, neurons that are responsive to loads. Fortunately, a major technical advance by Fetz and co-workers [59,60] now permits neural activity in the spinal cord to be recorded in awake behaving non-human primates, providing an important window on neural processing at this crucial stage in the motor system. Such studies will not only illuminate neural processing and the functional role of the spinal cord during volitional tasks, but also indirectly improve our understanding of MI function.

Neural correlates in MI of higher level representations of global goals is also not surprising, given the neural responses in regions that project to MI, such as dorsal and ventral premotor cortex [46,47,61–64]. Neurons in dorsal premotor cortex (PMd) do not respond strongly to passive limb motion, and movement-related activity is relatively insensitive to changes in limb geometry [63]. As compared to MI, neural activity in PMd tends to be more independent of the limb used to generate movements [45•], which suggests that it plays a more abstract role in planning motor actions.

MI creates an important bridge to convert this spatial goal-related activity in premotor regions into descending motor commands to control the activity of spinal circuitry. Observations that many neurons in MI maintain the same directional tuning even when movements are made with

different wrist orientations suggests that these neurons reflect information about the goal of the task [28]. However, many of these neurons still modulate their magnitude of activity with different wrist orientations so that they reflect both extrinsic and intrinsic information on motor behavior, perhaps reflecting an important transition between global goals and descending commands to control spinal circuitry [3].

Computational techniques other than the population vector method can overcome bimodal distributions [12•,65,66]. Yet, the discussion above highlights the inherent richness in the information conveyed in the discharge pattern of MI neurons. It should not be surprising that attempts to extract population signals in MI related to a single variable like hand motion will be imprecise and prone to errors, particularly when extrapolating from one motor context to another.

Efforts to create population signals from cortical activity remains an important and formidable problem for the emerging field of neuroprosthetics [67,68]. Several recent studies have illustrated the potential of using brain signals, such as simultaneous recording of multiple neurons in MI, to control robotic devices or re-animate paralyzed limbs [69–73]. The goal of these studies is largely focused on the development of neuro-assistive technology, but they also provide an interesting window on the adaptive capabilities of MI function [67,69,70]. Success in estimating parameters from population signals is likely to improve by matching the signal of interest with the type of information normally conveyed in a given cortical region. Therefore, global information related to spatial targets or the direction of intended motor action will be easier to estimate from neural activity in dorsal premotor and parietal cortex, whereas information related to limb geometry or force will be better estimated from MI [71]. Adaptive changes in neural activity as artificial motor actions are learnt will also assist the ability to develop and use neuroprosthetics [70].

Substantial improvement in our understanding of MI function may require experimental approaches beyond the traditional analyses of neural discharge rate. Recent studies have recorded the activity of multiple neurons simultaneously, providing the opportunity to explore how interactions between neurons are related to shared motor fields [74•,75] and motor performance [76,77]. These challenging experiments provide an opportunity to observe how processing within MI circuitry may underlie highly adaptable motor behavior.

Motor behaviors induced by stimulation in primary motor cortex

The generally accepted view of MI is that it possesses a rather coarse somatotopic representation, in which a given region of cortex reflects only a small portion of

the peripheral motor apparatus [5,78,79]. A very different perspective on the role and organization of MI has recently been put forward by Graziano and co-workers [4*,80]. They found that microstimulation of MI of non-human primates using high currents (25-150 μ A) and long durations (500 ms) evoked complex motor behaviors, such as whole-arm movements towards the mouth combined with a closing hand grasp and mouth opening. Stimulation at sites across the cortex revealed a map of spatial locations of near-body space to which movements were directed towards.

Although this is an intriguing observation that has already generated discussion [81,82], an important question is how intra-cortical stimulation relates to the activity of neurons during natural behavior. For example, neural activity in the superior colliculus creates a motor map of the direction and magnitude of eye movements. Stimulation at a site on the map elicits eye movements of a specific magnitude and direction, which parallels the normal response of neurons at this site. In other words, stimulation at a site that elicits 10° saccades to the left is also the site at which neurons maximally discharge for 10° leftward movements during natural behavior.

A key feature that has emerged from the work of Graziano and co-workers is that stimulation at a particular cortical site always elicits movements to the same final posture regardless of the initial limb configuration (i.e. hand motion to the mouth whether the initial position of the hand was to the left, right or straight out in front of the animal). Does the activity of individual neurons in primary motor cortex reflect such end-point equilibrium positions? The work of Caminiti and co-workers [83] suggests that neural activity during movement does not reflect such equilibrium positions. Non-human primates made reaching movements in different spatial directions, but from one of three different initial hand positions (left, right and central). In some cases, reaching movements were made to the same spatial location. They found that most neurons were broadly tuned to the direction of movement for movements initiated from each spatial location. Furthermore, although there were some changes in the directional tuning of neurons among initial hand positions, such changes appeared to maintain a constant orientation relative to body or shoulder orientation. They did not find neurons that changed their tuning functions such that the cell was maximally active for movements to the same spatial location, as expected if neural activity specified a final limb posture. In addition, recent work has shown that there is only a modest similarity in the directional tuning of neurons at a single location in MI, with no evidence of an organized representation of movement direction across the cortical surface [84]. Why there is such a substantial difference between the activity of neurons during natural behavior and motor actions created from long-trains of stimulation remains an open and interesting question.

Conclusions

This review highlights studies on neural activity in MI of non-human primates performing goal-directed limb motor tasks. This work illustrates two key points about this cortical region. First, neural activity in MI does not reflect a single, simple coordinate frame or representation. Rather, neural activity reflects many features of motor performance from high-level goals to low-level details of motor execution. Second, this complex representation of motor action in MI is not surprising when one considers the large number of cortical and subcortical regions that project and influence motor cortical activity as well as MIs important role for influencing brainstem and spinal circuitry to control movement. Although further neurophysiological studies on MI activity will certainly shed more light on its role in motor control, studies on neural activity in other parts of the motor system, such as the spinal cord, during volitional motor tasks will have an equally important impact on interpreting MI function.

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