

From Intention to Action: Motor Cortex and the Control of Reaching Movements

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Abstract The motor cortex was experimentally identified more than a century ago using surface electrical stimulation and lesions. Those first studies initiated a debate about the role of the motor cortex in the control of voluntary movement that continues to this day. The main issue concerns the degree to which the descending motor command emanating from the motor cortex specifies the spatiotemporal form of a movement or its causal forces, torques and muscle activity. The neurophysiological evidence supports both perspectives. This chapter surveys some of that evidence, with particular focus on the latter, more ‘traditional’, role of motor cortex.

The Discovery of the “Motor” Cortex

In the latter part of the 19th century, advances in anesthetic and surgical techniques finally permitted researchers to perform invasive experiments on animals that were in reasonably good physiological condition. Exploiting these new methods, first Fritsch and Hitzig and then Ferrier reported that electrical stimuli applied to the surface of a limited expanse of the cerebral cortex of several mammalian species evoked movements of parts of the contralateral body (for an excellent review of their studies, see Taylor & Gross 2003). They also showed that experimental lesions in that part of the cortex often resulted in motor deficits, including paralysis of parts of the body, after the animals recovered from surgery. These findings revealed that the cerebral cortex was electrically excitable and that a specific region of the cerebral cortex, the “motor” cortex, was implicated in the control of movement. Those seminal discoveries provided arguably the first solid experimental support for the localization of different functions in specific regions of the cerebral cortex.

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Their studies also initiated a debate about the nature of the representation of movement in the motor cortex that continues to this day (Taylor & Gross 2003). Fritsch and Hitzig used brief trains of stimuli and described the resulting motor responses as spastic twitch-like contractions of one or a few muscles. In contrast, Ferrier used longer-duration stimulus trains and reported evoked responses that looked like coordinated multi-joint fragments of natural behaviors such as orienting, feeding, defensive or aggressive actions. The central issue raised by their findings is whether the role of the motor cortex is better understood in terms of the targeted control of the contractile activity of groups of muscles or in terms of the higher-order planning and organization of coordinated actions. This chapter will provide a selective review of neurophysiological studies relevant to this debate. First, however, it is useful to survey some anatomy and conceptual issues.

Some Essential Anatomy

The most well known descending cortical projection in mammals is the corticospinal (CS) pathway to the spinal cord. The cells of origin of the CS tract are located across a broad expanse of cortex, including not only the primary motor cortex (M1) but also the premotor cortex and the postcentral cortex (Dum & Strick 1991; Picard & Strick 2001).

The majority of CS axons in primates, and all CS axons in other mammals, synapse on interneurons in the intermediate laminae of the spinal cord that are implicated in a range of reflex and pattern-generating functions. As a result, much (primates) or all (other mammals) of the descending CS influence on muscle activity is mediated indirectly by modulation of the activity of spinal interneuronal circuits. The fact is often overlooked in studies of arm movements.

In monkeys, apes and humans, an increasing number of CS axons also project into the spinal ventral horn and synapse on the dendrites of many spinal motoneurons within the motor pool that innervates a muscle (Shinoda et al. 1981; Picard & Strick 2001). Some of these “cortico-motoneuronal” (CM) axons only innervate the motor pool for a single muscle. However, the terminal arborizations of most CM axons diverge and synapse in the motor pools of several agonist muscles that act across one or more contiguous limb joints, but rarely across non-contiguous joints (Cheney & Fetz 1980; Cheney et al. 1985, 1991; Fetz & Cheney 1980; McKiernan et al. 1998; Park et al. 2004; Porter & Lemon 1993). Often, they also synapse on interneurons that exert an inhibitory influence on muscles that are functional antagonists of the muscles on which the CM neuron has an excitatory effect (Cheney et al. 1985). As a result, the discharge of a single CM neuron tends to establish a coordinated pattern of excitation and inhibition in a ‘muscle field’ of agonist and antagonist muscles (Bennett & Lemon 1996; Cheney & Fetz 1980; Cheney et al. 1985, 1991; Fetz &

Cheney 1980; McKiernan et al. 1998; Park et al. 2004). However, the synaptic strength of a single CM input is modest, so that the influence of a given CM neuron on the contractile activity of its muscle field is at best statistical, altering the probability that the motor units (the spinal motoneurons and their target muscle fibres) innervated by the CM axon will contract for a few milliseconds after the arrival of a CM action potential (Cheney et al. 1991; Porter & Lemon 1993). Overt contraction of a muscle requires convergent input from many CM axons and other synaptic inputs.

The terminations of CS axons on spinal interneurons and motoneurons provide a solid anatomical foundation to support a causal role for M1 in the control of muscle contractile activity. The direct CM projection onto spinal motoneurons in primates complements but does not replace the indirect CS projection onto spinal interneuronal circuits. Finally, spinal motoneurons also receive powerful synaptic inputs from several other descending pathways, and muscle activity is ultimately the product of all those convergent inputs, not just the M1 input.

Another important finding is that M1 is not anatomically uniform. Corticospinal neurons are found throughout M1, but CM neurons are located almost exclusively in the caudal part of M1 that lies in the rostral bank of the central sulcus (Rathelot & Strick 2006). Both rostral and caudal M1 receive inputs from the basal ganglia and the cerebellum, via the thalamus. However, the basal ganglia projection is stronger in caudal M1 and the cerebellar projection is concentrated in rostral M1 (Middleton & Strick 2000; Picard & Strick 2001). These anatomical gradients support the existence of a corresponding gradient of functional properties of neurons across M1.

Some Essential Concepts and Terminology

Many psychophysical and theoretical modeling studies have tried to infer how the motor system plans and executes arm movements. Concepts that have emerged from this work have had a major influence on the study and interpretation of M1 neural activity.

The first concept is that movement planning involves a hierarchical series of steps to transform the goal of a motor act, such as to reach to an object at a spatial location, into the appropriate pattern of arm muscle activity. This is often described as a series of coordinate transformations between different sets of sensory inputs and motor output parameters in different coordinate frameworks. For instance, the most explicit robotics-inspired planning models suggest that the initial stage in planning a reaching movement involves the specification of the final end point, spatial hand path, direction, distance, and speed of the hand from its current position to the target location. In subsequent steps, the motor system determines the pattern of joint rotations to displace the hand along the intended spatial trajectory, then the joint torques necessary to produce those joint rotations, and finally the activation signals to the muscles

acting across each joint (Flanders et al. 1992; Hollerbach 1982; Kalaska & Crammond 1992; Kalaska et al. 1997; Soechting & Flanders 1989, 1992).

These ‘brute-force’ planning models make a useful distinction between different classes of motor parameters. One is between *extrinsic* or *hand-centered* spatial parameters that describe how the hand is moving in or interacting with the environment, and *intrinsic*, *joint-centered* or *muscle-centered* parameters that describe events at specific parts of the limb. Another is between the spatiotemporal form of movement (its *kinematics*) and its underlying causal forces and muscle contractile activity (its *kinetics*). Finally, *static* parameters describe the motor system at equilibrium (e.g., stable postures and forces), whereas *dynamic* parameters describe the time-varying form (e.g., direction and rate of change of hand spatial position or joint rotations) and forces of movements.

The hierarchical coordinate transformation hypothesis has been very influential but it should not be taken too literally. It was inspired in part by early engineering studies of controllers for multi-joint robots, that viewed motor control as fundamentally a problem of Newtonian mechanics that is achieved by solving equations derived from the laws of motion and trigonometry. However, it is much more likely that the design of biological motor systems is based on natural principles determined by the properties of peripheral sensors and effectors rather than by Newtonian and Euclidian formalisms. There are also theoretical grounds to argue that the motor system cannot completely and explicitly pre-plan the moment-to-moment details of the extrinsic and intrinsic kinematics of an intended movement, and then implement the kinematic plan by computing the requisite instantaneous kinetics. Nevertheless, the coordinate transformation hypothesis has heuristic value if taken in a more metaphorical sense as a convenient language to capture the general nature of the information encoded in neural activity. I will use those terms in that more symbolic sense.

This large class of models in which motor planning culminates in the generation of descending motor cortical output commands that specify the required movement kinetics and muscle activity are often called *force-control* models. An alternative class, called *position-control* models, rejects the idea that the motor system controls movement by explicit planning and control of output kinetics (Feldman 1986; Feldman et al. 1990; Feldman & Latash 2005; Feldman & Levin 1995; Flash & Hogan 1985; Foisy & Feldman 2006; Ostry & Feldman 2003). In contrast, they propose that the central motor system generates simple, relatively monotonic, signals about the desired final equilibrium state of the limb at which all external forces are balanced by internal muscular viscoelastic forces. In position-control models, the time-varying details of movement kinematics and kinetics are not explicitly planned or controlled. They emerge at the periphery as a result of the interplay between monotonic control signals, spinal reflex circuits and the inherent viscoelastic mechanical properties of muscles.

Position-control models can replicate many aspects of the psychophysics of motor behavior (Adamovich et al. 1997; Feldman 1986; Feldman et al. 1990; Feldman & Latash 2005; Feldman & Levin 1995; Ghafouri & Feldman 2001; Flash & Hogan 1985; Foisy & Feldman 2006). Nevertheless, virtually all

neurophysiological studies of M1 have been guided by and interpreted in terms of force-control models. They have sought to determine the degree to which M1 neural activity is correlated with different parameters of motor output, such as its kinematics versus kinetics or its extrinsic versus intrinsic parameters. These studies assume that M1 functions like a controller that specifies a particular parameter of the desired output, and that the descending output from M1 is a command signal that controls that parameter of the resulting motor response.

Microelectrode Recordings: M1 Neuronal Coding of Movement Parameters

In the 1950's, Herbert Jasper pioneered the use of 'chronic' extracellular micro-electrode recordings of the temporal discharge patterns of single neurons in unanaesthetized animals in different natural behavioral states. This method has its limitations. For instance, it does not provide direct access to information processing or information storage mechanisms that are not directly expressed in action potentials, such as sub-threshold post-synaptic potentials, modulation of presynaptic function, molecular signaling cascades, or the regulation of protein synthesis or gene expression. Nevertheless, this method has provided much of what we know about the real-time neural mechanisms underlying brain functions.

Coding Movements at a Single Joint

Ed Evarts was the first to use chronic recordings to study neural activity in M1 in behaving monkeys trained to perform simple motor tasks such as back-and-forth movements of a single joint (Evarts 1968, 1969). He showed that single M1 neurons were maximally active during movements of one joint but less active or inactive for other joints. Furthermore, neurons discharged maximally during one direction of movement of the preferred joint and were less active or suppressed for the opposite direction. This activity typically began 50–150 msec before the onset of agonist muscle contractions. Other researchers also showed that M1 activity varied with such parameters as static joint angles, and the direction, amplitude and speed of joint rotations (for review, see Porter & Lemon 1993; Ashe 1997). These seminal studies showed that M1 neurons generated signals that provided specific information about the nature of movements of specific body parts prior to their initiation.

Single-Joint Versus Whole-Arm Movements

Most of those early studies used single-joint tasks. The assumption was that parametric coding of motor output could be best studied by reducing movement

to its most 'elemental' unit, rotation about a single joint. However, most natural behaviors require multi-joint movements. Generating a multi-joint movement involves more than a simple linear combination of isolated single-joint rotations. On the contrary, multi-joint movements introduce a number of control problems that do not arise in single-joint tasks. One is the 'surplus degrees of freedom' problem. For instance, there are more degrees of freedom of rotation of the joints of the arm than there are parameters needed to define the spatial location and orientation of the hand. Similarly, the hand can move along a theoretically infinite number of paths between two locations, and the arm can assume many different postures while moving along each path. Typically, there are more muscles exerting forces across a given joint than there are degrees of freedom of torque or rotation of that joint. As a result, a desired joint rotation or level of net torque across a joint can be generated by a theoretically infinite combination of different levels of contraction of agonist and antagonist muscles. A different problem arises from the mechanics of multi-joint motions. Because major body segments such as the arm are chains of masses linked by joints, movement of one limb segment will generate interaction forces that act on adjacent limb segments. If these interaction forces are not counteracted, arm movements would have a whippy, 'wet-noodle' character.

Coding of Whole-Arm Reaching Movements by Single Neurons and Neural Populations

An influential study of M1 activity during whole-arm reaching movements was performed by Georgopoulos and colleagues (1982). Monkeys made reaching movements in 8 directions in a 2D plane to targets arrayed in a circle around a central start location. The activity of single M1 neurons related to proximal-arm movements varied systematically and gradually for a wide range of reach directions, resulting in a relatively broad, continuous and symmetric directional tuning curve that was centered on a preferred direction for each neuron (Fig. 1a). Different neurons had different preferred directions, and all potential movement directions away from the starting position were represented relatively uniformly in the sampled neural population.

These findings showed that during a reach in any given movement direction, many neurons with a broad range of different preferred directions were active to varying degrees. This implied that an unambiguous signal about the direction of movement was embedded in the distributed pattern of activity of the entire active population. To test this idea, Georgopoulos et al. (1982, 1983) represented the activity of each neuron by a vector whose direction was always aligned along the neuron's preferred direction but whose length varied as a function of the mean level of discharge of the neuron during each movement. When the activity of all neurons during each movement was represented as a set of single-neuron vectors, the resulting vector distributions showed a strong

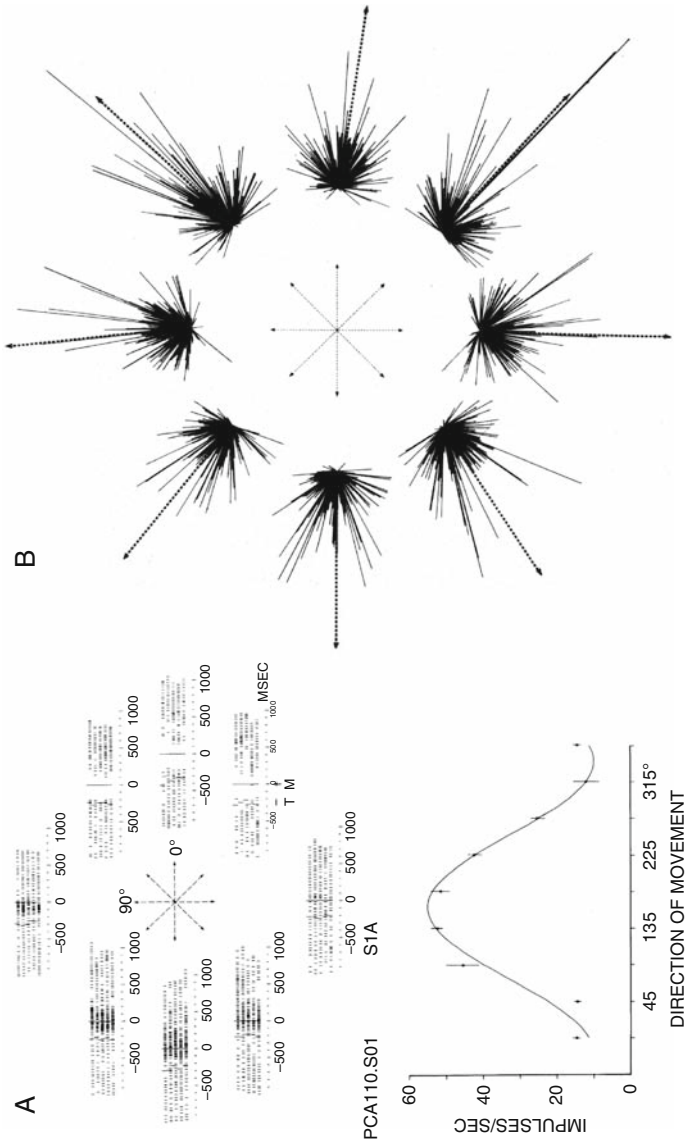


Fig. 1 *A Top-* raster plots of the activity of an M1 neuron during 5 movements in 8 different directions in a 2D plane, aligned to the onset of movement ('M'). *Bottom-* the directional tuning curve for the same neuron, centered on its preferred movement direction, calculated from the mean discharge rate of the neuron from the appearance of the target to the end of movement. **B** Vectorial representation of the distribution of directional activity in an M1 neural population during 8 directions of movement. Single-neuron vectors (*thin lines*) are aligned to each neuron's preferred movement direction and the length is scaled according to the mean discharge rate of the neuron from the appearance of the target to the end of movement for each movement direction. *Thick dashed arrows* are the net population vectors, calculated by vectorial addition of all single-neuron vectors in each cluster. Note how the directional bias of the activity of the M1 population shifts systematically with movement direction. (reproduced with permission from Georgopoulos et al. 1982 **A** and Georgopoulos et al. 1983 **B**)

directional bias that shifted systematically with movement direction (Fig. 1b). When all the single-neuron vectors for a direction were summed, the net resultant vectors were oriented closely along the actual executed movement directions (Fig. 1b).

They subsequently extended these findings to 3D space and into the time domain, during reaching movements from the center to the 8 corners of a cubic work space (Georgopoulos et al. 1988; Schwartz et al. 1988). The summed population activity at each successive 20-msec time interval varied systematically with movement direction in 3D space, starting from about 100 msec before movement onset until the end of movement (Fig. 2a). When the 20-msec population vectors were joined tip to tail, the resultant 'neural trajectories' corresponded well with the actual spatial hand paths of the reaching movements to each target (Fig. 2b) (Georgopoulos et al. 1988).

These properties of M1 neural activity have been confirmed repeatedly in many subsequent whole-arm movement studies that revealed correlations between neural activity and extrinsic spatial parameters such as movement direction, target location, and movement distance, speed, and tangential velocity during straight-line reaching movements and figural tracing movements (Fig. 3)

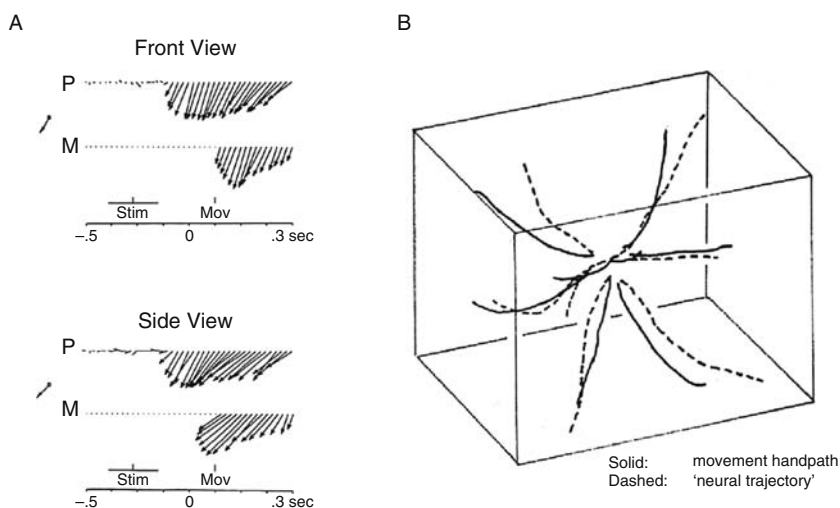


Fig. 2 **A** Front and side views of the instantaneous movement velocity of the hand in 3D space (M), and the net population vector of M1 neural activity (P), calculated every 20 msec from 500 msec before movement onset to 300 msec after movement onset, for movements to the lower left front corner of a cubic workspace. **B** The movement hand paths (solid lines) and the 'neural trajectories' of M1 activity (dashed lines) during arm movements from the center to the corners of a cubic workspace, reconstructed by joining the 20-msec movement and neural-population vectors **A** tip to tail. Note how the summed activity of the M1 population varies systematically with the extrinsic spatial trajectory of 3D arm movements. (modified and reproduced with permission from Georgopoulos et al. 1988)

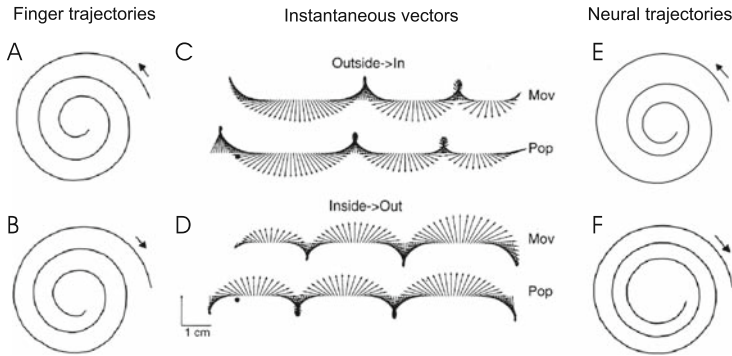


Fig. 3 **A, B** Mean spatial path of the finger during many repeated trials of an inward **A** and outward **B** spiral tracing task. **C, D** Vector representation of the temporal sequence of instantaneous velocity of displacement of the finger (**Mov**) and of the net directional population signal in M1 (**Pop**) at equally spaced brief time intervals along the path of inward and outward spiral tracing movements, respectively. **E, F** Neural trajectories during inward and outward spiral tracing movements, reconstructed by joining the instantaneous population vectors **C, D** tip to tail. Note the close correspondence between the moment-to-moment activity of the M1 neural population and the extrinsic spatial kinematics of figural tracing motions of the hand. (modified and reproduced with permission from Moran & Schwartz 1999b)

(Ashe & Georgopoulos 1994; Fu et al. 1993, 1995; Koike et al. 2006; Moran & Schwartz 1999a,b; Paninski et al. 2004a,b; Schwartz 1993, 1994).

These findings suggested that the broad directional tuning curves of M1 neurons were a fundamental property by which they encoded motor output parameters. The single-neuron vector notation implied that each time a neuron increased its activity, it exerted a directional influence that tended to displace the arm along its preferred direction. The strength of that influence was maximal at the neuron's preferred direction and decreased as the angular difference between the neuron's preferred direction and the desired movement direction increased. The correspondence between the direction of population vectors and movement indicated that the direction of motor output was determined by an approximately linear summation of the directional influences of all active neurons. The results all suggested that M1 generated a detailed representation of the moment-to-moment spatiotemporal trajectory of arm movements that was expressed in terms of the extrinsic spatial kinematics of hand motion, including its instantaneous direction, speed and tangential velocity (Figs. 2, 3). This would place M1 fairly early in the putative motor control hierarchy, defining the overall form of limb movements rather than the mechanical details of their implementation.

However, if the M1 motor command for arm movements is a veridical replica of hand motion through Cartesian space, it is not clear why the neural correlations with spatial kinematics account for only a part of the total variance of task-related neural activity (Paninski et al. 2004a,b; Wu & Hatsopoulos 2006). It is also not obvious how to reconcile such a high-level motor command with the CS

projection from M1 onto spinal segmental interneurons and motoneurons. The following sections review studies that attempted to identify which motor output parameters could account for the greatest amount of task-related variance in M1 activity, by using tasks that dissociated different sets of output parameters.

Representation of Extrinsic Versus Intrinsic Motor Output Parameters in M1

Although the reaching and figural tracing tasks explicitly controlled hand displacement in extrinsic space, they also produced equally broadly tuned changes in all parameter spaces associated with joint rotations, forces, and muscle activity. The shoulder and elbow joints undergo approximately sinusoidal variations in their extent and rate of rotation as a function of the direction of hand displacement (Graham et al. 2003; Kalaska et al. 1989, 1990; Scott & Kalaska 1997). Proximal-arm muscle contractile levels vary broadly with the direction of hand displacement (Georgopoulos et al. 1984; Kalaska et al. 1989; Kurtzer et al. 2006). The broad muscle tuning curves in turn reflect how the level of causal forces and torques they exert across joints varies with the direction of hand displacement. As a result, the directional tuning curves of M1 neurons when expressed in hand-centered spatial coordinates are not of themselves conclusive evidence that they are coding the hand-centered extrinsic spatial kinematics of movement. They could instead reflect the control of motor output at the joint or muscle level (Mussa-Ivaldi 1988; Scott & Kalaska 1997; Todorov 2000; Ajemian et al. 2000, 2001). A series of studies have attempted to address this issue by decoupling the extrinsic spatial parameters of hand motions from intrinsic joint- and muscle-centered parameters.

Reaching in the Same Direction but in Different Spatial Locations

Caminiti et al. (1990, 1991) expanded on the study by Georgopoulos et al. (1988) by training monkeys to make 3D reaching movements from the center to the corners of 3 adjacent cubic work spaces, one directly in front of the monkeys and the other cubes immediately to the left and right of the central cube. If M1 neurons encoded the hand-centered spatial kinematics of whole-arm movements from the centers to the corners of each cube, their activity should be identical in the 3 work spaces. In contrast, they found very few neurons with constant directional tuning across all cubes. Typically, the preferred direction and amplitude of the 3D tuning functions of most M1 neurons changed from cube to cube, and neurons were often directionally tuned in some of the cubes but not in others. Across the sample population, there was a systematic net rotation of the preferred movement directions of the tuning curves from one cube to the next about the vertical axis, that corresponded

well with the rotation of the shoulder joint about the vertical axis while the monkey moved its arm in the 3 cubes. Caminiti et al. (1990, 1991) concluded that single M1 neurons encoded the directionality of whole-arm motor output in a shoulder-centered coordinate system.

Wu and Hatsopoulos (2006; see the chapter by Reimer & Hatsopoulos (2008) in this volume) recorded M1 activity while monkeys made random sequences of reaching movements between targets on a horizontal rectangular grid, and then constructed directional tuning curves for each neuron in each quadrant of the grid. Like Caminiti et al. (1990, 1991), they found that many but not all M1 neurons were directionally tuned throughout the grid. The preferred direction of a few neurons remained constant in all sectors of the grid, consistent with a hand-centered extrinsic spatial coordinate system. Also like Caminiti et al. (1990, 1991) they found that the tuning curves of most other neurons rotated in the horizontal plane when the hand was in different parts of the grid, suggesting that their activity was influenced by arm posture-dependent intrinsic movement parameters. For some neurons, the tuning tended to be constant in shoulder-centered spatial coordinates or in joint-centered intrinsic coordinates. Overall, however, none of the models accounted for the directional tuning changes of the majority of the M1 neurons.

Nevertheless, both Wu and Hatsopoulos (2006) and Caminiti et al. (1990, 1991) showed that the directional tuning functions of M1 neurons changed when monkeys made reaching movements in the same spatial directions but in different quadrants of the arm's range of motion. This would not be expected if M1 neurons signaled only the hand-centered direction of reaching movements.

Reaching Along the same Hand Paths but Using Different Arm Postures

Scott and Kalaska (1997, Scott et al. 1997) used a different approach to decouple extrinsic and intrinsic movement parameters, by exploiting the surplus degrees of freedom of arm movements. Monkeys made reaching movements in 8 directions in a 2D horizontal plane at shoulder level while holding their arm either in its "natural" parasagittal posture or with the arm abducted into the horizontal plane with the elbow at the same level as the shoulder and hand (Fig. 4). The hand paths of the reaching movements were identical when the arm was in either posture but both the joint motions and muscle activity changed between arm postures (Scott & Kalaska 1997). If M1 neurons encoded motor output in hand-centered extrinsic spatial coordinates, their activity should not be altered by the change in arm posture. The degree to which their activity changed between the two arm postures would provide an estimate of the degree to which it was modulated by intrinsic motor output parameters.

They found the change in arm posture caused significant changes in the discharge of many single M1 neurons, including either the preferred direction

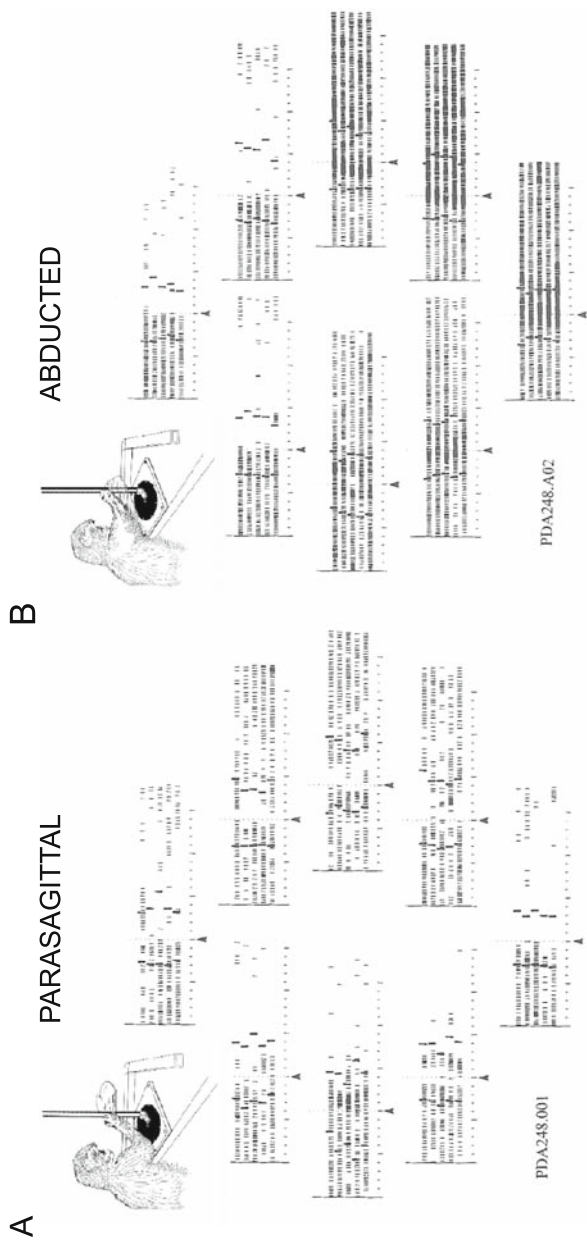


Fig. 4 Raster plots of the activity of a single M1 neuron during reaching movements in 8 directions in a 2D horizontal plane, with the arm in the natural parasagittal plane **A** and with the arm abducted up into the horizontal plane at shoulder level **B**. Note the increased tonic activity, and greatly enhanced discharge during movements along the same spatial hand paths to the targets in the lower right quadrant when the arm was in the abducted posture **B** than in the parasagittal posture **A**. (modified and reproduced with permission from Scott & Kalaska 1997)

or amplitude of their tuning curves, or both (Fig. 4). These changes indicated a correlation of neural activity with the posture-dependent change in intrinsic movement parameters as the hand moved along the same spatial paths. The posture-dependent effects were stronger in M1 than in the adjacent premotor cortex (Scott et al. 1997). However, the effect of arm posture was not as strong on average on M1 neural activity as it was on muscle activity, nor was it as strong as that predicted by simulations of the responses of neurons that encoded pure joint-centered or muscle-centered output parameters (Scott & Kalaska 1997).

Changes in arm posture also altered the overall distribution of preferred directions of M1 neurons (Scott & Kalaska 1997). When the arm was in the parasagittal posture, the distribution of preferred directions of shoulder-related neurons was relatively uniform, as had been seen in earlier studies using the same arm posture (Georgopoulos et al. 1982, 1988; Schwartz et al. 1988). However, when the arm was rotated into the abducted posture, the distribution became skewed. Modeling simulations suggested that this change in preferred direction distribution was due to the effect of arm posture on shoulder joint motions and muscle activity. Reaching movements in the parasagittal posture involve shoulder joint rotations in all three degrees of freedom (flexion-extension, abduction-adduction, and external-internal rotation about the long axis of the humerus). However, when the arm was in the horizontal plane, shoulder motions are strongly reduced in the axis of external-internal rotation, which would cause the hand to move in and out of the horizontal plane of the reaching movements. The change in preferred direction distributions reflected the reduction of M1 neural activity associated with that degree of shoulder rotation. This finding was later corroborated in a study that found an even more strongly skewed preferred direction distribution in a task that strictly constrained limb motions to the horizontal plane (Cabel et al. 2001; Gribble & Scott 2002).

The consensus of these studies is that many proximal arm-related M1 neurons generate signals that are modulated by intrinsic motor output parameters. They are locally tuned but not globally tuned for the direction of motor output. Their activity changes whenever the arm changes posture, whether to move the hand in different parts of space or to move the hand along the same spatial path while using different arm postures. However, the neurons also show a wide range in their sensitivity to arm posture, and a greater proportion of neurons are relatively uninfluenced by arm posture than one might expect by chance. This indicates that while the M1 movement representation reflects to some degree the intrinsic joint- or muscle-centered parameters of reaching movements and so is not exclusively extrinsic in nature, it is probably not exclusively intrinsic either.

Kakei et al. (1999, 2001, 2003) exploited the surplus degrees of freedom of wrist joint motions to decouple extrinsic and intrinsic motor parameters. Monkeys made wrist movements in 8 constant spatial directions in a vertical plane while holding the wrist and forearm in either fully pronated, fully supinated or intermediate postures. Many wrist-related M1 neurons showed significant changes in directional tuning in different wrist-forearm postures. However, a slight majority of M1 neurons were relatively unaffected, as were most neurons

in ventral premotor cortex. The more modest posture-dependent effects in M1 seen by Kakei et al. (1999,2001, 2003) during wrist movements, compared to the findings of the arm reaching studies, may be due to technical differences in task design, biomechanics or data analysis, but may also indicate a real difference in the M1 representation of proximal and distal arm movements.

Representation of Kinematics Versus Kinetics of Motor Output in M1

Another long-standing question concerns the degree to which M1 activity encodes the spatiotemporal kinematics or the underlying causal kinetics of movement. The literature on this issue is very extensive (for an excellent review, see Ashe 1997).

Direction of Rotation Versus Force at Single Joints

Once again, Evarts did the pioneering work (1968, 1969). Monkeys held a hinged handle and made alternating flexion-extension movements of the wrist. A pulley and weight system decoupled kinematics from kinetics by applying a force to the handle to pull it either in flexion or extension. This external load required a change in the level of forces and contractile activity of wrist flexor and extensor muscles (variable kinetics) during the wrist movements (constant kinematics). For example, wrist flexor muscles actively contracted during normal unloaded wrist flexions and relaxed during extensions. When the load opposed flexion by pulling the wrist towards extension, the flexor muscles had to contract more strongly during flexion movements to overcome the external load. In contrast, when the load assisted flexion by pulling the wrist in that direction, the flexor muscles were much less active than during unloaded flexion movements. Evarts found that the discharge of many M1 neurons was strongly altered by the loads in parallel with the changes in kinetics and muscle activity required to move against the loads. The neurons were signaling not just what to do (kinematics) but also providing information about how to do it (kinetics).

The same property of M1 activity was shown in isometric tasks in which monkeys controlled the direction and level of output forces across a stationary joint. Many M1 neurons changed their activity as a function of the direction and level of isometric output forces, which required changes in the contractile activity of muscles but did not result in movement (Evarts et al. 1983; Ashe 1997).

In a prescient study, Humphrey et al. (1970) showed that the appropriately weighted sum of the activity of a small group of neurons was better correlated to the dynamic forces required to produce wrist movements than the activity of a single neuron. This was arguably the first evidence for a population coding mechanism for motor output parameters in M1.

Fetz and Cheney (1980, Cheney & Fetz 1980) extended this line of study to CM neurons that made monosynaptic contact with spinal motoneurons. They found that many CM neurons projecting onto wrist muscles showed systematic variations in activity as a function of motor output forces during a wrist movement task. Similar findings were reported for CM cells projecting onto wrist, finger and intrinsic hand muscles during a precision-pinch task of the thumb and fingers (Bennett & Lemon 1994; Hepp-Reymond et al. 1999; Maier et al. 1993).

A broad consensus that emerged from single-joint studies was that the discharge of many M1 neurons covaried with parameters of motor output kinetics. Nevertheless, it was also clear that the response properties of M1 neurons were as heterogeneous in the domain of kinematics versus kinetics as they were for extrinsic versus intrinsic parameters. The activity of a significant number of M1 neurons in every study was well correlated to the kinematics of a task but poorly correlated to its kinetics. This heterogeneity was well illustrated by a study in which monkeys made a repeated sequence of wrist flexion-extension movements between three static postures (flexed, intermediate, extended), either while unopposed by an external load or against extension or flexion loads (Thach 1978). The discharge of many M1 neurons varied systematically with the changes in muscle activity required to make the movements and to hold the wrist in the static postures against the loads. However, the activity of a nearly equal number of neurons signaled the current static postures and movement directions independent of the forces or muscle activity the monkeys had to exert. Finally, another sizeable population of M1 neurons signaled the anticipated direction of the next movement in the sequence, rather than the current posture, movement or output forces.

Force is a vector with direction and length (magnitude). Neurons whose activity varied with output kinetics often showed a non-linear correlation with the output force vector (Ashe, 1997). For instance, many neurons showed a stronger correlation with the direction of the force vector than its length. Correlations with force magnitude were often monotonic at low force levels, but activity saturated at an intermediate level and did not increase further as the animal exerted increasingly greater levels of force. Some neurons, including CM cells, showed a paradoxical decrease in activity as a function of increasing force magnitude (Hepp-Reymond et al. 1999). In summary, single-joint studies showed that task kinetics has a strong influence on the discharge of many but not all M1 neurons. It is also clear that M1 activity does not provide a simple linear, veridical representation of output kinetics during single-joint actions.

Coding of Kinematics Versus Kinetics During Whole-Arm Motor Tasks

Far fewer studies have systematically examined the M1 representation of output kinetics in multi-joint tasks. Kalaska et al. (1989) revisited the issue during whole-arm reaching movements. Their task replicated the Evarts (1968, 1969) study, but expanded it from one dimension of single-joint rotations to two

dimensions of reaching movements in a horizontal plane. Monkeys moved a handle in 8 directions away from a central starting position. A pulley-and-weight system could apply a force to the handle in any one of the 8 movement directions. The monkeys had to exert a force component against the handle in the direction opposite to that of the applied load while continuing to reach in the different movement directions. The task manipulated output kinetics in the directional domain but not in the magnitude domain, because the size of the load was constant. The kinematics of the reaching movements to the 8 targets were identical across all load conditions (Kalaska et al. 1989). This task design permitted the study of M1 neural activity during 8 reaching movements with highly stereotypical kinematics under 9 different sets of kinetics conditions (no load, and 8 external load directions).

During unloaded movements in different directions, proximal-arm muscles showed the usual broadly tuned changes in contractile activity (Fig. 5a) (Kalaska et al. 1989). They also showed broadly tuned and continuously modulated changes in contractile level as a function of the direction in which the external load pulled the task handle (Fig. 5a). Although the external loads were applied to the hand, the proximal-arm muscle EMG patterns showed that the loads caused broadly tuned changes in the joint- and muscle-centered kinetics of motor output. Equally importantly, the EMG patterns showed that the monkeys did not compensate for the external loads by co-contracting all muscles to stiffen the limb. In contrast, they exerted skilled reciprocal control of antagonist muscles, to generate an extra force vector component in the direction opposite to the applied load while moving the arm in the different directions.

The activity of many proximal arm-related neurons in the caudal part of M1 strongly resembled the behavior of muscles (Fig. 5b, c). In particular, the neurons showed continuously graded changes in the level of reach-related activity when the monkeys performed the kinematically constant arm movements while compensating for the different directions of external loads. There was an overall increase in activity across all directions of movement when the external load pulled the handle in directions that opposed their preferred movement direction and a reciprocal decrease in task-related activity when the external load pulled the handle in their preferred direction (Fig. 5c). Intervening directions of loads caused intermediate degrees of change in task-related neural activity.

However, there was a broad range in the sensitivity of M1 neurons to the external loads, from neurons that were as strongly modulated as the muscles by both movement and load direction, to neurons that were strongly tuned for movement direction but were relatively insensitive to the presence and direction of external loads. Significantly, no neurons showed the opposite pattern of strong modulation with the direction of external loads but not of movement. Neurons were only sensitive to the external loads if they were also directionally tuned during unloaded arm movements, indicating a common functional contribution to both movement and the compensation for external loads.

This was further supported by the finding that the sensitivity of neurons to external loads was also coupled to their temporal pattern of activity during

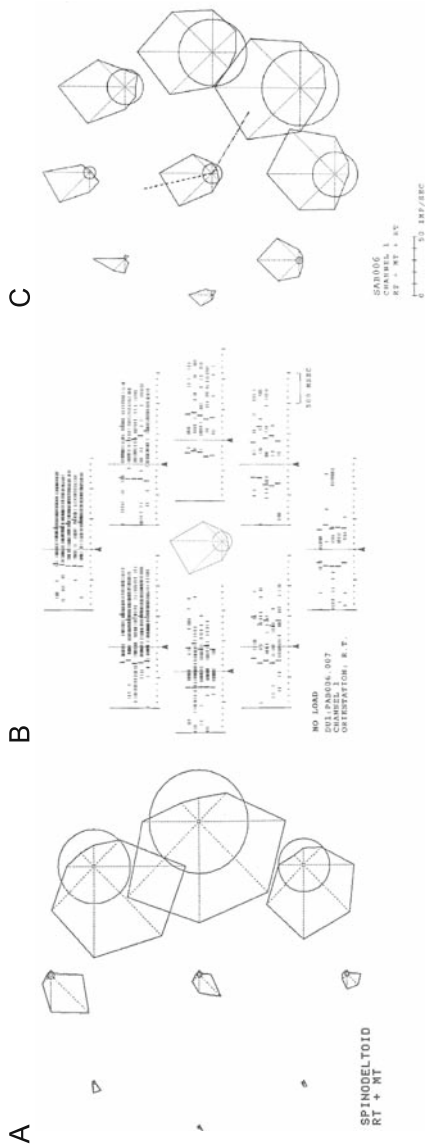


Fig. 5 **A** Polar plot representation of the contractile activity of the posterior deltoid muscle of the left arm during unloaded arm movements in 8 directions in a horizontal plane (*central polar plot*) and during movements in the same 8 directions against a load that pulls the arm in one of the 8 directions (*outer polar plots*). The position of each outer polar plot indicates the direction in which the load pulls the arm away from the central starting position. The length of each axis of the polar plots is proportional to the area under the rectified and averaged EMG envelope during 5 movements in each direction, and the radius of the circle in each polar plot is proportional to the mean EMG activity during postural hold at the central starting position prior to movement onset. The muscle is most active for movements to the lower left during unloaded arm movements (*central polar plot*). Task-related contractile activity is greatly increased when the external load pulls the handle to the right, opposite to the muscle's preferred movement direction (*rightward polar plots*) and is nearly completely suppressed when the load pulls the arm in the preferred direction of the muscle (*leftward polar plots*). **B** Raster plots of the activity on an M1 neuron during unloaded arm movements in 8 directions in the horizontal plane. Polar plot at the center illustrates the tuning curve of the neuron (same format as in **A**). **C** Polar plot representation of the activity of the same M1 neuron as in **B**, during unloaded arm movements in 8 directions (*central polar plot*) and during movements in 8 directions against an external load that pulls the arm in one of the 8 directions. Same format as in **A**. Note how the discharge of the M1 neuron is continually modulated as a function of the direction of movement and the direction of external loads, much like the proximal-arm muscle **A**. (modified and reproduced with permission from Kalaska et al. 1989)

unloaded arm movements. Neurons that were strongly modulated by external loads also showed large changes in tonic activity while the monkeys held their arm over the different target locations without the external load (Fig. 5b). In contrast, neurons that showed little sensitivity to external loads typically emitted directionally-tuned phasic bursts of activity prior to and during unloaded arm movements but relatively little posture-dependent activity. Finally, the majority of the most load-sensitive neurons were recorded from the caudal part of M1 in the bank of the central sulcus. Neurons in the more rostral part of M1 were less strongly modulated by external loads. These trends indicated that the sensitivity of neurons to the kinematics versus kinetics of motor output during reaching movements reflect some underlying functional organization within M1, rather than empirically acquired correlations that emerged within a randomly connected neural network during training.

Load-dependent responses were also evident at the population level (Fig. 6a). The population-vector signal varied systematically in direction and length during reaching movements against external loads in different directions. This showed that the net directional signal emitted by the caudal M1 population did not signal only the spatial kinematics of the arm movements across all load conditions. Instead, it also reflected the direction-related modulations in

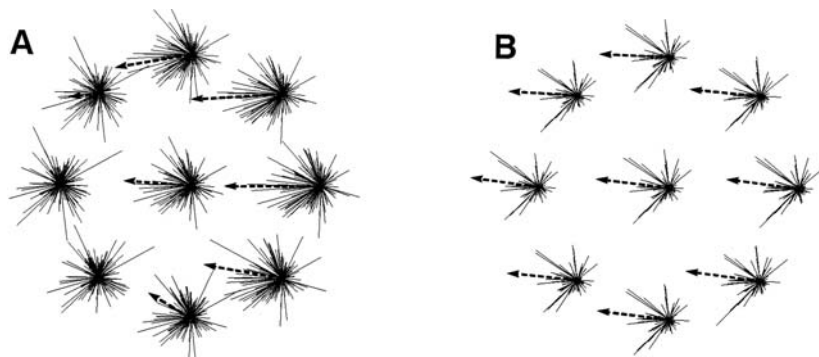


Fig. 6 **A** Vector representation of the activity of an M1 neural population during arm movements to the left, without an external load (*central plot*) and against an external load that pulls the arm in different directions (*outer plots*). The position of the outer vector plots corresponds to the direction that the load pulls the arm. Note how loads that oppose the leftward movement by pulling the arm to the right result in an increase in the strength of the leftward signal generated by the M1 population, whereas loads that assist the movement by pulling the arm to the left result in a substantial decrease in the strength of the leftward signal in M1. Note also that loads that pull the arm perpendicular to the leftward movement (*upper and lower vector plots*) result in a deviation of the net population signal in a direction that is opposite to the direction in which the load is pulling the arm. **B** Vector representation of the activity of a population of neurons in posterior parietal area 5 during arm movements to the left, without an external load (*central plot*) and against an external load that pulls the arm in different directions (*outer plots*). Same format as in **A**. Note how the area 5 population generates a strong leftward directional signal that is unaltered by the presence and direction of external loads. (reproduced with permission from Kalaska 1991)

kinetics required to produce the kinematically constant movements against the external loads.

The functional significance of these correlations with task kinetics in M1 was reinforced by recordings made in posterior parietal cortex area 5 in the same task (Fig. 6b) (Kalaska et al. 1990). Many area 5 neurons were broadly directionally tuned during reaching movements (Kalaska et al. 1983; 1990). However, most area 5 neurons showed little or no modulation of their movement-related activity during reaching movements against the external loads. The net population-vector signal also covaried with the direction of movement but showed little modulation with changes in task kinetics caused by the external loads (Fig. 6b). In contrast to M1, area 5 generated a representation of reaching movements that reliably reflected the unaltered kinematics of arm movements across a wide range of directional changes in the task kinetics.

Gribble and Scott (2002) directly tested the effect of joint-centered kinetics on M1 activity using a device that supported the arm in the horizontal plane during 2D reaching movements in different directions, and that could apply torques directly to the either the elbow or shoulder joint or simultaneously to both. The movement-related activity of many M1 neurons was altered by viscous (joint rotation velocity-dependent) torques applied to one or the other joint but not both, while others were affected by torques applied to both. They found similar neural correlates to joint-centered torques applied to the shoulder or elbow during a postural stabilization task (Cabel et al. 2001). These results showed that the single-neuron representation of arm movements in M1 could provide specific information about the joint-centered kinetics of motor output during multi-joint tasks.

Control of Output Forces During Whole-Arm Isometric Tasks

Isometric tasks in theory permit the study of the contribution of M1 to the control of task kinetics without movement-related confounds in neural activity. Georgopoulos et al. (1992) studied the control of the direction of whole-arm isometric output forces in the 2D horizontal plane. In each trial of the task, monkeys first generated a small static bias force at the hand in one of 8 directions, and then generated a rapid force pulse in one of 8 directions away from the initial static bias force. Many M1 neurons showed broad continuous tuning with the direction of the static bias forces or with the dynamic force pulses, or both, that were very similar to the directional tuning curves seen during reaching movements. However, the net population vector signal was correlated with the direction of the change in force during the force-pulse epoch of the task, but not with the total force output vector generated by the monkeys, which was the vectorial sum of the static bias force and the dynamic force pulse. The major conclusion of their study was that the M1 activity was primarily concerned with the control of changes in the direction of dynamic isometric whole-arm force outputs.

Taira et al. (1996) then examined the M1 activity from the Georgopoulos et al. (1992) study for correlations with both the direction and magnitude of the small initial bias forces exerted by the monkeys in all three spatial dimensions. They used an additive linear regression model with separate terms for direction and magnitude. Although force is a vector with both direction and magnitude, this model assumed that the motor system treats force magnitude as a non-directional scalar independent of force direction. Single neurons typically showed broad 3D tuning curves as a function of isometric bias force direction. While many neurons showed strong correlations with the direction of the static force vector, very few showed correlations with its non-directional magnitude. This contrasted with the behavior of arm muscles recorded in the task, a small majority of which were significantly modulated by both the direction and non-directional magnitude of output forces. Those findings were later corroborated by Boline and Ashe (2005) in another whole-arm isometric force task in which both the direction and magnitude of the output force were controlled. They also found that the vast majority of M1 neurons were tuned for the direction of isometric force output but unmodulated by force magnitude, using either additive or multiplicative regression models. The consensus of these three isometric-force studies was that M1 was implicated in the control of the directionality of isometric output but was not explicitly signaling the desired isometric output force vector.

Consistent Correlations with Output Kinetics Across Different Tasks

The studies by Georgopoulos et al. (1982, 1988, 1992), Taira et al. (1996) and Boline and Ashe (2003) also suggested that the directionality of motor output in whole-arm isometric-force and reaching tasks was coded by similar broad tuning curves. Sergio and Kalaska (2003; Sergio et al. 2005) examined this directly by comparing the activity of the same M1 neurons in both a 2D horizontal isometric force task and a 2D reaching task. Unlike the other studies, they controlled and confined the vertical forces exerted by the monkeys to a narrow range about the horizontal plane of the tasks.

In the isometric-force task, monkeys generated isometric force ramps in 8 different constant spatial directions in the horizontal plane, while holding their hand in one of 9 different spatial locations arrayed in a circular workspace in the horizontal plane. Each spatial location of the hand required a different arm posture. While generating the forces at any one hand location, proximal-arm muscles showed the usual broad directional tuning (Fig. 7a). Their contractile activity was also highly sensitive to arm posture, showing a systematic variation in directional bias, depth of tuning and overall magnitude across the different hand locations (Sergio and Kalaska 2003) (Fig. 7a). These modulations in contractile activity while generating spatially constant isometric output forces at the hand reflected the changes in such intrinsic biomechanical factors as the

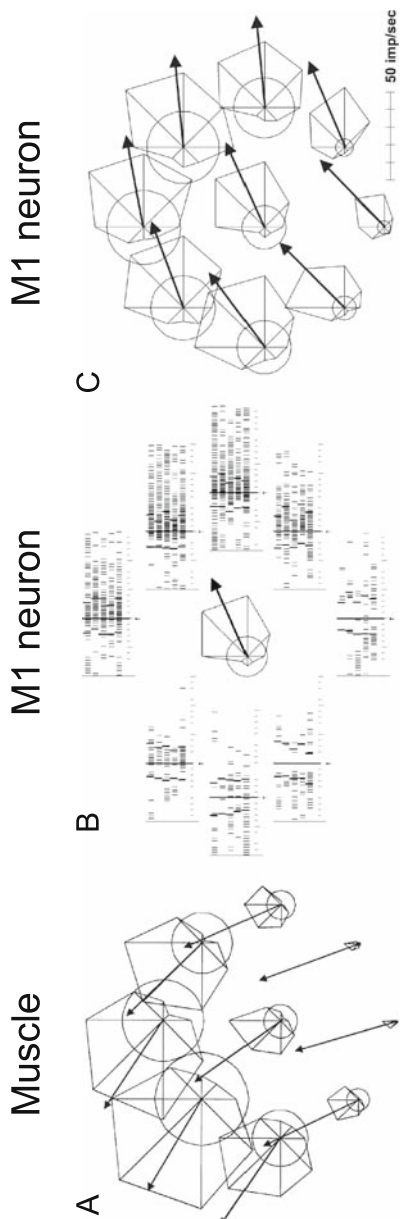


Fig. 7 A Polar plot representation of the contractile activity of the right anterior deltoid muscle during isometric force generation in 8 directions in a horizontal plane with the hand at a central workspace location (*central plot*) and in 8 other spatial positions on a circle of 8 cm radius in the horizontal plane (*outer plots*). Note how the force direction-related contractile activity of the muscle varies systematically in strength and directional tuning as a function of the spatial location of the hand and associated changes in arm posture. B Raster and polar plot representation of the activity of an M1 neuron during isometric force generation in 8 directions in the horizontal plane with the hand at the central workspace location. C Polar plot representation of the activity of the same M1 neuron as in B, during isometric force generation in the central workspace location (*central plot*) and in 8 other spatial locations on a circle of 8 cm radius in the horizontal plane (*outer plots*). Same format as A. Note how the isometric force direction-related activity of the M1 neuron varies systematically in strength and directional tuning as a function of hand workspace location and arm posture, in a manner that is very similar to that of the proximal-arm muscle. (reproduced with permission from Sergio & Kalaska 1997 A and Sergio & Kalaska 2003 B, C)

moment arm, pulling angle and length/tension properties of muscles as the arm changed posture (Kurtzer et al. 2006).

Many neurons in caudal M1 were broadly tuned with isometric force direction at each hand location (Fig. 7b,c) (Sergio & Kalaska 2003). Many of the neurons also showed systematic changes in the preferred direction, depth of tuning and overall level of activity as the monkeys generated constant isometric forces at different hand locations, that resembled the posture-dependent changes in muscle activity. This indicated that M1 activity was modulated by intrinsic motor output attributes during isometric force generation, consistent with earlier findings during arm movements (Caminiti et al. 1990, 1991; Scott & Kalaska 1997; Gribble & Scott 2002; Wu & Hatsopoulos 2006). Nevertheless, the activity of other M1 neurons was relatively unaffected by changes in arm posture during isometric force production.

The same neurons were also recorded during reaching movements from a central starting position to 8 targets (Sergio et al. 2005). Unlike prior reaching studies, the task handle was weighted and imposed a substantial inertial load during movement. To move the handle accurately between the targets, the monkeys had to apply an initial accelerative force onto the handle that was directed towards the target, but then had to momentarily reverse force direction to decelerate the handle as it approached the target (Fig. 8b). This resulted in a momentary dissociation between the direction of the kinematics and kinetics of motor output during movement. The temporal dynamics of force outputs in the movement task were quite different from the isometric task, in which the output forces increased monotonically towards the final target level without a transient reversal (Fig. 8a).

Proximal-arm muscle activity changed as expected between the two tasks to generate the different dynamic force patterns. They showed gradual ramp-like changes in contractile activity in the isometric task, but showed the classic 'triphasic' response pattern during the inertially-loaded arm movements (Fig. 8a,b). This included an initial agonist burst followed by a momentary pause in activity during movements in the preferred direction of the muscles, and a transient delayed burst of activity during movements in the opposite direction as the muscles generated a brief braking force pulse to slow the movement. The triphasic EMG patterns showed that the transient reversal of net output forces at the hand required to accelerate and then decelerate the task handle was paralleled by corresponding transient reversals of forces and torques at proximal arm joints.

Many proximal arm-related M1 neurons showed a corresponding change in discharge pattern between the two tasks (Sergio et al. 2005). In the isometric task, the neurons usually showed abrupt changes in tonic activity, often accompanied by an initial transient burst-like overshoot of activity prior to force onset in their preferred direction (Fig. 8a). In contrast, during the reaching movements against an inertial load, many of the M1 neurons showed response patterns that resembled to a first approximation the triphasic EMG patterns, including the agonist burst and transient pause in the neuron's preferred direction and the delayed 'antagonist' burst in the opposite direction (Fig. 8b). These

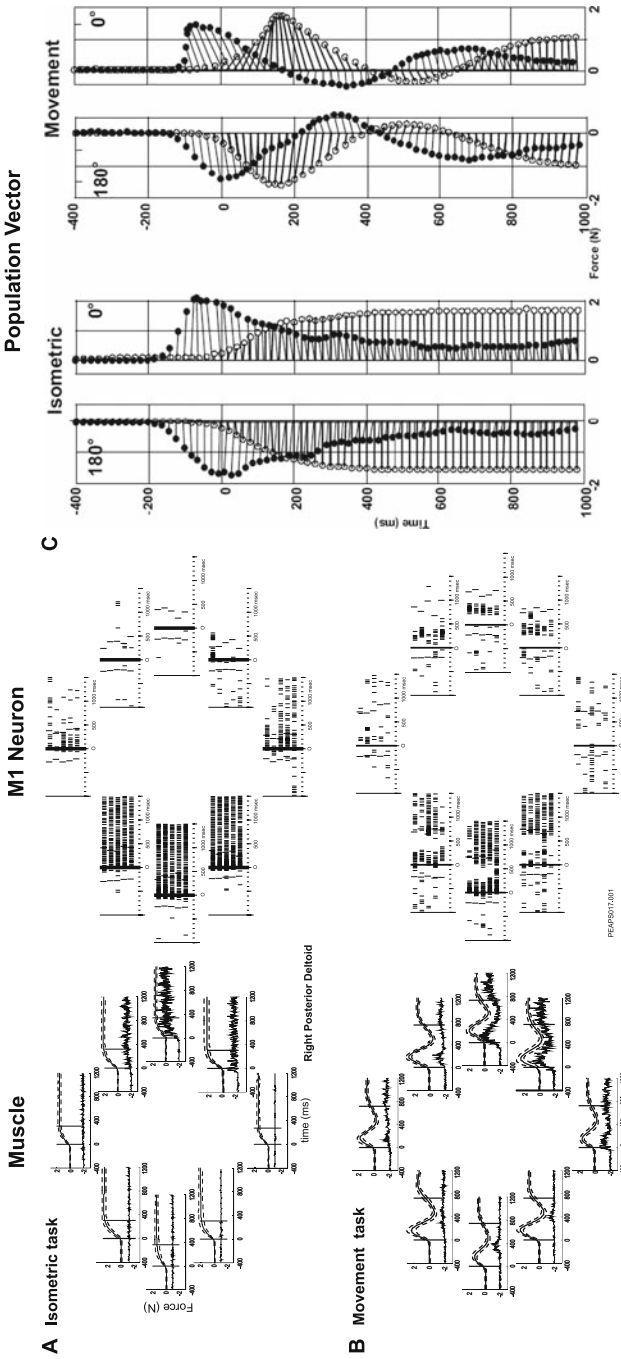


Fig. 8 A Histograms of the mean contractile activity of the right posterior deltoid muscle (*left*) and rasters of the activity of an M1 neuron (*right*) during isometric force generation in 8 directions in the horizontal plane at the central workspace location. Traces above the EMG activity show the time course of the force ramp applied by the hand onto the rigid isometric handle in 8 directions. **B** Histograms and rasters of the activity of the same muscle and M1 neuron during arm movements in 8 directions. Traces above the EMG show the force applied by the hand onto the moving handle in 8 directions. Note how the EMG and M1 neural activity changes from a monotonic step in the isometric task to a 'triphasic' pattern in the movement task, paralleling the changes in the time course of forces applied to the task handles in the two tasks. **C** Instantaneous force output vectors (*open circles*) and M1 neural population vectors (*solid circles*) calculated every 20 msec during isometric force generation (*left*) pair of columns of vectors) in the directions to the *right* (0°) and to the *left* (180°), as well as during arm movements (*right* pair of columns of vectors) in the same two directions. Time progresses downward. Note how the M1 population vectors capture the time course of the directionality of force output in both tasks, including the transient reversal of forces during the movement task. Note also how the length of the population vectors is greater during the dynamic (time-varying) phase of each task than during the final static force phase. (modified and reproduced with permission from Sergio & Kalaska 1998, and Sergio et al. 2005)

dynamic response components in the neural activity typically preceded the reversal of output forces by about 200 msec.

Importantly, virtually every task-related M1 neuron was active in both the isometric and reaching tasks. There was no evidence for a significant population of M1 neurons that was mainly or only active in one or the other of the two tasks.

Correlates of the differences in dynamic forces in the two tasks were also evident at the population level. Net population vectors generated from the task-related activity every 20 msec pointed in the direction of the force target at all times in the isometric task (Fig. 8c). In the movement task, in contrast, the vectors first pointed towards the intended target prior to movement onset, then rapidly reversed to point approximately in the opposite direction, before rotating back towards the intended target as the hand approached the target (Fig. 8c). The population signal in caudal M1 was therefore much more closely related to the temporal dynamics of the direction of output kinetics required to produce the reaching movements than it was to the directional kinematics of the resultant movements. The reversal of the population vector occurred well in advance of the reversal of the measured output forces at the hand and of the onset of the antagonist burst in EMG activity.

In summary, these single-neuron and neural-population findings by Sergio et al. (2005) implicated M1 neurons in the bank of the central sulcus in the control of output kinetics across a broad range of motor behaviors, including static and dynamic forces during both isometric and movement tasks.

However, some features of the neural activity were not correlated to parameters of output kinetics. One of the most prominent was the initial burst-like overshoot in activity in the isometric task, which had also been seen in many prior studies (e.g., Fetz & Cheney 1980). There was no correlate of this initial overshoot in either the measured output forces or EMG activity, both of which showed a gradual ramp-like increase to the final static target level. This was also clear in the population vector signals, which showed a much more prominent representation of the initial dynamic phases of both tasks than the final static force output phases (Fig. 8c).

Neural correlates of task kinetics were far less evident in parietal area 5 (Hamel-Pâquet et al. 2006). Unlike M1, many area 5 neurons were strongly directionally tuned during arm movements but inactive in the isometric task (Fig. 9a,b). Both tasks required precise control of muscle activity and output forces, but many area 5 neurons were only active when the muscular forces caused limb movements. Furthermore, there was no single-neuron or population-level correlate of the transient reversal of output forces during reaching movements in area 5 (Fig. 9c). These findings in the temporal domain corroborated the earlier findings in the directional domain (Kalaska et al. 1990) that area 5 generated a representation of arm movements primarily in terms of its kinematics. The distinctly different properties of area 5 and M1 activity in identical task conditions also further validated the functional significance of

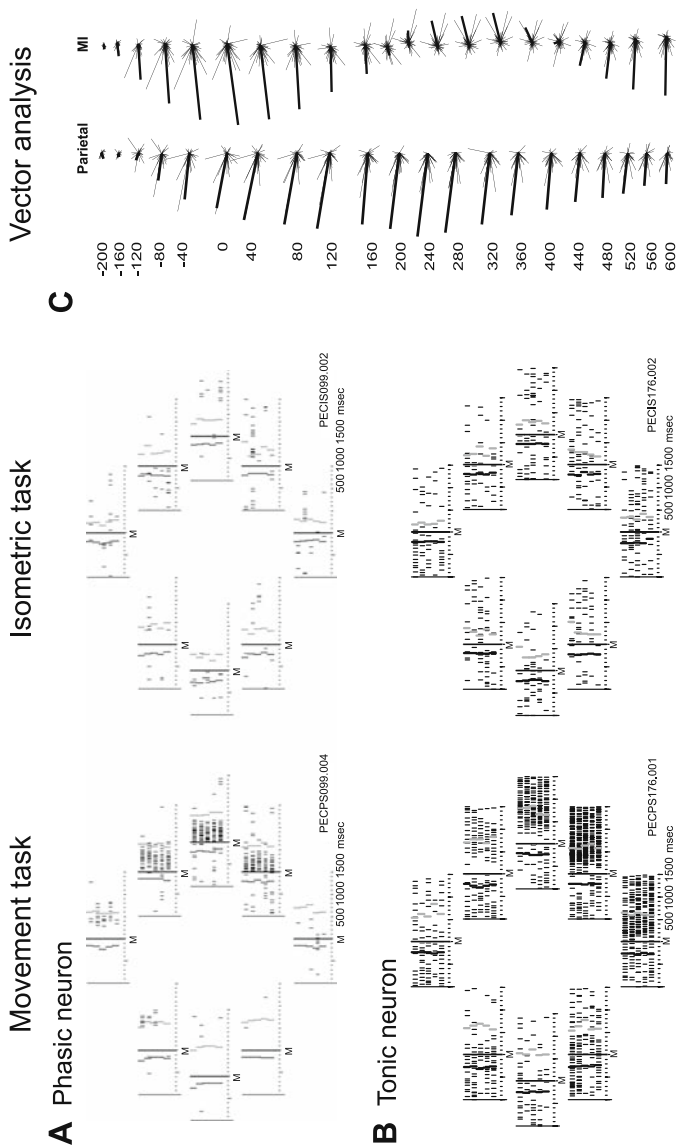


Fig. 9 A, B Raster representations of the activity of two different posterior parietal area 5 neurons during arm movements (*left*) and isometric force generation (*right*) in 8 directions in the horizontal plane. Note the strong directional tuning in the movement task and the near complete loss of task-related activity during the isometric force task. **C** Population vector representation of the activity of an area 5 neural population during arm movements to the left (*left column*) and of an M1 neural population during arm movements to the left in the same task. Note how the area 5 population signal is oriented consistently in the direction of displacement of the arm, whereas the M1 population shows a transient reversal in the direction of their neural activity during movements in the identical task conditions. (reproduced with permission from Hamel-Pâquet et al., 2006)

the M1 correlates with the dynamic pattern of kinetic output parameters during whole-arm isometric and movement tasks.

Neural Correlates with Muscle Activity in M1

Muscles generate the causal forces and torques underlying motor behavior. The neural correlates of output kinetics in M1 may be an indirect effect of a primary role of M1 in the control of muscle activity. Indeed, the hypothesis that M1 directly controlled muscle activity was first proposed almost as soon as the motor cortex itself was identified, and was widely accepted as its principal role in the neurological and neurophysiological literature for many years.

Nevertheless, fewer studies have searched for M1 neural correlates of muscle activation signals than for other motor parameter, in part because establishing a causal link between M1 activity and muscle activity is technically challenging. Ideally, one would want to know the muscles to which a neuron's activity is targeted. However, most M1 neurons do not project to the spinal cord. Only a minority of M1 neurons are corticospinal neurons, and most of those synapse on spinal interneurons. Identification of the targeted muscles is feasible for CM cells, but even then, one can never be certain that one has identified all the muscles of the CM cell's muscle field. For all other M1 neurons, evidence for muscle-specific control signals is correlational in nature, as is the case for the relation of M1 activity to any other output parameter.

Similarities between the directional and temporal activity patterns of muscles and neurons across a wide range of task conditions (Georgopoulos et al. 1984; Kalaska et al. 1989; Sergio & Kalaska 2003, Sergio et al. 2005; Scott & Kalaska 1997) provide circumstantial evidence that many M1 neurons in the bank of the central sulcus generate signals that may specify muscle activation levels or could be readily transformed into muscle-specific signals in the spinal cord. In particular, Sergio et al. (2005) found single-cell and net population correlates of the temporal dynamics of task kinetics and of the triphasic EMG activity required to produce rapid inertially-loaded arm movements. The reciprocal 'braking' response in M1 clearly preceded the antagonist burst in the muscles and the decelerating forces at the hand, supporting a causal role for M1 in the generation of the antagonist response. In contrast, position-control models propose a spinal reflex origin for the decelerating component of the triphasic EMG response (Adamovitch et al. 1997; Feldman 1986; Feldman et al. 1990; Feldman & Latash 2005; Feldman & Levin 1995; Ghafouri & Feldman 2001; Ostry & Feldman 2003). Nevertheless, Sergio et al. (2005) did not establish a direct causal link between M1 neural activity and muscle activity, or show that the M1 activity explicitly encoded muscle contractile levels.

Other studies reported that M1 activity is correlated with the contractile activity of small groups of muscles but not with others in a variety of tasks (Georgopoulos et al. 1984; Holdefer & Miller 2002; see also Morrow et al.

2008, this volume). These groupings do not appear to be random, but rather involve muscles that are functionally related, suggesting that single M1 neurons may control the activity of muscle synergies rather than the activity of any one muscle.

Still other studies have reconstructed the mean temporal pattern of muscle contractile activity and even its trial-to-trial variability from the appropriately weighted summed activity of small sets of M1 neurons (Morrow & Miller 2003; Carmena et al. 2003; Santucci et al. 2005; Townsend et al. 2006). These analyses showed that there is sufficient information in the activity of M1 neurons to extract a signal that could potentially control muscle activity. Santucci et al. (2005) extracted neural signals correlated with EMG activity not only from M1 but also from premotor, postcentral and posterior parietal cortex. However, the correlations may have had different origins in the different cortical areas and do not imply that all of those cortical areas contributed equally to the direct control of muscle activity (Santucci et al. 2005).

As was the case for other motor parameters, there are also many features of M1 activity that do not correlate well with muscle activity. For example, some M1 neurons discharge during instructed-delay periods when there is no overt change in EMG activity. Furthermore, in virtually every study, many M1 neurons did not respond to experimental manipulations in the same way as muscles, in particular, showing less sensitivity overall to output kinetics and intrinsic mechanics than muscles (e.g., Ashe 1997; Evarts 1968, 1969; Kakei et al. 1999, 2001, 2003; Kalaska et al. 1989, 1990; Scott & Kalaska 1997; Sergio & Kalaska 2003; Sergio et al. 2005; Thach 1978).

Of all M1 neurons, only CM cells have a direct synaptic influence on spinal motoneurons, and might be expected to be the most closely implicated in the control of muscle activity. A few studies have examined the degree to which CM neurons signal explicit information about the contractile level of muscles in its muscle field (Bennett & Lemon 1994, 1996; McKiernan et al. 1998, 2000). The consensus is that there is no simple relationship between the activity of CM neurons and their target muscles. While the activity of CM neurons often covaries with the contractile activity of one or more muscles in their muscle field, there are many exceptions to that trend. For instance, while some CM neurons show a positive linear relation to output force and to the contractile level of their target muscles, others show a negative relationship (activity decreases with increasing force) and still others show no consistent relation at all (Bennett & Lemon 1994, 1996; Hepp-Reymond et al. 1999; McKiernan et al. 1998, 2000).

Finally, CM neuron activity can show a context-dependent relationship to motor output (Hepp-Reymond et al. 1999). CM cells were often more active when monkeys made carefully controlled reciprocal wrist movements or precise pinches with the thumb and index finger than during more forceful agitated back-and-forth wrist movements or during power-grip tasks to exert large forces on a handle, even though the contractile level of the muscle fields of the

CM neurons was substantially greater in the latter, less precisely controlled tasks (Cheney & Fetz 1980; Cheney et al. 1985; Muir & Lemon 1983).

In summary, there is evidence that some M1 neural activity is correlated more or less closely with muscle contractile activity. This is difficult to reconcile with hypotheses that M1 generates a representation of higher-order spatial parameters of motor output that is then transformed into muscle activation signals in the spinal cord. However, the discharge of many other M1 neurons is poorly correlated with muscle activity. Even CM neurons often show a complex and variable relationship with the contractile activity of their target muscles. If M1 plays a major role in controlling muscle activity, it does so by mechanisms other than a large population of M1 neurons that explicitly signal the activation levels of muscles to spinal motoneurons across all task conditions.

Ultimately, specific muscle activation signals are generated only at the level of the spinal motoneurons themselves. Spinal motoneurons and interneurons receive convergent monosynaptic inputs from many supraspinal sources, including corticospinal, rubrospinal, reticulospinal, vestibulospinal and tectospinal pathways. The activity of spinal motoneurons is determined by the combined effect of those convergent descending signals and local spinal interneuronal inputs, all of which affect the correlation of M1 activity with motor output parameters, including muscle activity.

Back to the Beginning: What does the Motor Cortex do, and How?

The motor cortex was the first area of the cerebral cortex for which a specific function was identified by neurophysiological experiments, more than a century ago. Nevertheless, its role in the control of movement is still not fully resolved. Recordings of neural activity during a wide range of motor tasks have found evidence for representations of an equally wide range of motor output parameters, from high-order hand-centered spatial kinematics to low-level joint-centered forces, torques, and muscle activity. The activity of many other neurons does not fit neatly into any parameter space or coordinate framework. Why has this seemingly simple question been so difficult to answer? We can answer that question by posing several more specific questions.

Are We Looking at the Right Movement Parameters?

One critical issue is the choice of parameters and coordinate frameworks used to analyze neural activity. Virtually all studies have correlated neural activity with the convenient but arbitrary parameters and coordinate axes of Newtonian mechanics. As noted earlier, however, biological motor systems evolved to control a musculoskeletal mechanical system with sensors and

effectors (muscles) that have unique properties. Joint torque is a Newtonian mechanical parameter that defines the rotational force required to produce a particular joint motion. However, in biological motor systems, joint torque is a pooled parameter that reflects the summed mechanical effect of a combination of muscle contractions. It is highly unlikely that an M1 neuron knows what a Newton-meter is or how to calculate how many Newton-meters are needed to generate a particular movement. The same reservation applies to correlations between neural activity and the velocity or acceleration of a desired movement. Nevertheless, the peripheral motor plant is a physical system that must obey the universal physical laws captured by the Newtonian equations of motion. Therefore, it is highly likely that neurons that are implicated in the control of the spatiotemporal form of a movement or its causal muscle activity will show statistical correlations with different sets of Newtonian mechanical parameters of kinematics and kinetics even if they are performing computations based on completely different principles. Even the output signal of a position-control system will inevitably show statistical correlations with task kinetics because it must generate the kinetics required to produce a desired movement indirectly via dynamic or static dissociations between the actual and signaled equilibrium state of the limb (Feldman & Levin 1995; Foisy & Feldman 2006). Therefore, even if one identifies a correlation between M1 activity and different Newtonian parameters, this does not mean that one has necessarily identified the true nature of the parameter spaces and coordinate frameworks encoded in M1 neural activity. On the other hand, the correlations are not meaningless because they can help identify what general properties of the motor output are being processed by a given neuron or neural population.

How can We Deal with Statistical Coupling Between Movement Parameters?

Experimental design is another critical issue. A fundamental problem in the interpretation of neural activity is a strong statistical coupling between different classes of motor output parameters during movement. Reimer and Hatsopoulos (2008, this volume) provide a thoughtful discussion of this issue. I would like to reinforce that point, and add some others.

Because of the laws of motion, anatomy and musculoskeletal biomechanics, any movement will create correlations among different classes of motor output parameters. For instance, a given direction and speed of hand movement will involve a particular combination of elbow and shoulder rotations and will be caused by a particular combination of direction and magnitude of muscle contractions and output forces across each joint. Because most neural recording studies are correlational in nature, the interpretation of any observed correlation between neural activity and a particular experimentally-controlled

parameter is confounded by the inevitable correlations between that parameter and others (Reimer & Hatsopoulos 2008).

This problem also applies to efforts to identify muscle activation signals in M1. For instance, statistical correlations between the activity of an M1 neuron and the contractile activity of several muscles are consistent with the control of muscle synergies by single M1 neurons (Holdefer & Miller 2002). However, the validity of this inference is limited by the fact that the contractile activity of many muscles is also statistically correlated during a task because of anatomy, functionally overlapping muscle actions, and the stereotypical coupling of motions at different joints during whole-arm movements (Georgopoulos et al. 1984; Soechting & Flanders 1992). One must eventually find more direct experimental evidence of synaptic effects of the recorded neuron in the motor pools of multiple muscles, as is done to identify CM neurons.

Similarly, Santucci et al. (2005) extracted signals that resembled EMG contractile envelopes from neural activity in several cortical areas including the posterior parietal cortex, even though experiments deliberately designed to decouple output kinematics and kinetics found relatively little co-variation of activity with task kinetics in parietal cortex (Kalaska et al. 1990; Hamel-Pâquet et al. 2006). As Santucci et al. (2005) noted, however, their finding only showed that there is enough of the appropriate time-varying information in the neural activity to extract a signal that resembles an EMG envelope once all other sources of discharge variance have been averaged out. The neurons in each area may be encoding other parameters of movement, but an EMG-like signal can be extracted because of the inherent statistical coupling between muscle activity and other movement parameters. Such findings may not provide as much of an insight into the movement representation in M1 as they provide a demonstration of the power of linear reconstruction methods to replicate a target waveform (e.g., the temporal pattern of a motor output parameter) from a sufficiently large set of time-varying neural signals, especially if the latter are encoding parameters that are themselves statistically correlated with the target waveform. This reservation applies to all reconstructions of signals correlated with motor output parameters during unperturbed arm movements. This does not mean that the findings are automatically invalid, only that they must be interpreted with that caveat in mind.

A brute-force approach to cope with statistical coupling would be to try to manipulate independently or otherwise account for all possible parameters of movement in one experiment, ranging from hand-centered extrinsic spatial kinematics to the contractile patterns of every muscle, right down to the unique length/tension and force/velocity properties of each muscle. Ultimately, this is experimentally intractable. A more practical approach is to design tasks that decouple motor parameters in a limited number of dimensions of the full multi-dimensional parameter space of motor output, and to observe whether neural activity follows more closely one or the other of the decoupled parameters. It is also very informative to look for differential effects of those manipulations on

neural responses in different cortical areas. This approach does not eliminate the problem of statistical coupling, but it does reduce it within the manipulated dimensions of the task, improving the inferential power of the experiment. Many studies of motor output coding in M1 have not taken adequate measures to decouple different classes of output parameters, which has undoubtedly contributed to the diversity of their findings.

To What Degree are We Observing the Motor Command or its Sensory Consequences?

Another likely source of confounds in M1 activity is peripheral sensory input. Correlational studies try to identify the nature of the centrally-generated “feed-forward” motor output command from M1. However, many M1 neurons receive short-latency inputs from muscle spindles and other somatic receptors, and their activity is modulated by that reafferent sensory input during movement. This input does not serve only the classic “feedback” roles of movement monitoring and the detection and correction of errors during movement itself. It also modulates activity across M1 as a function of the current state of the limb, including its posture and movement, which will in turn produce appropriate state-dependent alterations of the motor output commands for future movements (Burnod et al. 1999; Kalaska & Crammond 1992). Experimentally, it is difficult to disentangle feedforward output commands from sensory feedback signals in M1 neural activity once muscle contractions and movement begin, to distinguish between a central or peripheral origin for an observed neural correlation with a motor parameter. Ultimately, however, any signal that modifies the activity of M1 descending output neurons, whether central or peripheral in origin, becomes a component of the motor command.

Is M1 Functionally Homogeneous or Diversified?

Another issue is whether M1 has one unifying function that applies equally well to all neurons in all parts of M1. There is considerable evidence to challenge that idea. As reviewed earlier, there are significant differences in the anatomical connectivity of the rostral and caudal parts of M1. Neural response properties also appear to vary between the rostral and caudal parts of the motor cortex (Crammond and Kalaska 1996, 2000). Many of the neurons that show the strongest correlations with intrinsic motor parameters and with motor output kinetics are concentrated in the caudal part of M1 located in the bank of the central sulcus (Kalaska et al. 1989; Scott & Kalaska 1997; Sergio & Kalaska 2003; Sergio et al. 2005). It is noteworthy that the multi-electrode arrays used in recent studies to record the simultaneous activity of populations of M1 neurons are implanted on the surface of the precentral gyrus and do not record from neurons

in the bank of the central sulcus (Carmena et al. 2003; Hatsopoulos et al. 2004; Paninski et al. 2004a, b; Taylor et al. 2002; Serruya et al. 2002; Wessburg et al. 2000). The nature of the motor output command from that part of M1 may not be identical to that generated by M1 neurons in the bank of the central sulcus.

Does M1 Control the Spinal Motor Apparatus, or Advise it?

Because lesions of M1 in higher primates and man lead to severe motor deficits or complete paralysis, it is natural to assume that M1 plays the dominant role in initiating and controlling voluntary movements. Another implicit assumption of most studies is that M1 is a controller that specifies the spatiotemporal profile of a particular parameter of the desired motor output, which is then implemented at the spinal level. This perspective treats the spinal motor apparatus as essentially passive circuitry whose activity during voluntary movements is entirely imposed by descending motor signals. This ignores the inherent pattern-generating properties of spinal interneuronal and reflex networks. The spinal cord of most vertebrates, if not all, is capable of generating the complex patterns of muscle activity underlying basic locomotor rhythms. Studies of obstacle avoidance during locomotion in the cat suggest that M1 does not completely specify the kinematics or kinetics of modified stepping motions. Instead, it generates specific signals about the changes in the timing and intensity of muscle activity required to alter the normal gait to step over obstacles (Drew 1993). A similar functional relationship between M1 and the pattern-generating circuitry in the spinal cord may be retained during the control of voluntary arm movements in primates (Georgopoulos & Grillner 1989).

One Size may not Fit All: Does M1 have One Fixed Function or does it Adapt itself to the Needs of the Task?

Finally, it is necessary to consider the validity of another major assumption underlying most neurophysiological studies of motor control. These studies generally view motor control as a deterministic process in which M1 contains a set of neural circuits that perform a fixed and definable computation such as a sensorimotor coordinate transformation, to generate a signal that defines a specific kinematic or kinetic parameter of the desired movement, that is used to control motor behavior across a wide range of motor tasks. As already noted, position-control models reject this assumption and argue that control of movement is achieved via control of physiological processes such as muscle length-tension properties, stretch reflex recruitment thresholds, and reciprocal activation versus co-contraction of antagonist muscles (Feldman 1986; Feldman et al. 1990; Feldman & Latash 2005; Feldman & Levin 1995; Ostry & Feldman 2003).

Even so, position-control models also assume a fixed set of control parameters and neural operations underlying the control of motor output across a broad range of task conditions.

Paz and Vaadia (2008, this volume) describe a different perspective, in which M1 is an adaptive network whose neural response properties change as a function of the demands of different tasks. Rather than performing a pre-determined computation to generate a motor command, M1 and associated structures learn the input-output relationship between a desired end-state and the motor command required to achieve that outcome in the current task conditions. The adaptation process may involve a form of function approximation by linear summation of “primitives” or “basis functions” whose properties are reminiscent of the tuning curves of M1 neurons (Donchin et al. 2003; Hwang et al. 2003; Hwang & Shadmehr 2005; Shadmehr 2004; Thoroughman & Shadmehr 2000). Psychophysical and modeling studies of function approximation of the coordinate transformation between forces and motions predict changes in the preferred direction and gain of the tuning functions of the basis functions (Ajemian et al. 2000, 2001; Kakei et al. 2003; Hwang et al. 2003; Hwang & Shadmehr 2005) that are strikingly similar to the changes in M1 single-neuron tuning curves seen while generating motor outputs in different arm postures or against different loads (Kakei et al. 2003; Kalaska et al. 1989; Scott & Kalaska 1997; Sergio & Kalaska 2003). However, those neurophysiological experiments also found many similar effects on muscle activity. It will be a difficult experimental problem to determine to what degree those M1 neural responses represent a central computational process of function approximation or are simply imposed by anatomy and biomechanics.

The adaptive neural circuits may be organized into modules, or “internal models”, that use combinations of sensory feedback and efference copies of outgoing motor commands to learn to mimic the dynamical properties of the motor plant and its interactions with the environment (Bhushan & Shadmehr 1999; Haruno et al. 2001; Hwang & Shadmehr 2005; Kawato 1999; Shadmehr 2004; Wolpert & Kawato 1998; Wolpert & Miall 1996). Forward internal models learn to predict what arm movement will result from a given motor command, whereas inverse internal models learn the opposite association between a desired motion and the motor command required to generate it. Computationally, internal models perform sensorimotor coordinate transformations, but the underlying mechanisms are more biologically realistic than earlier hypotheses that assumed some form of neural implementation of the solution to equations derived from Newtonian mechanics. The observed neural correlates with both higher-order kinematics and with causal kinetics would implicate M1 as a component of an internal inverse dynamics model that transforms a representation of the desired form of the movement into signals to control its causal details.

An intriguing new perspective comes from recent “optimal feedback control” models (Harris & Wolpert 1998; Todorov & Jordan 2002; Todorov 2004; Scott 2004). An optimal feedback controller does not attempt to control a

specific parameter of movement. Instead, it seeks to implement the optimal control scheme for each task by minimizing variability and errors in the output parameters that are the most critical for accomplishing the goal of the task. The nature of the control scheme and the critical sources of feedback signals will vary according to the demands of each task, such as precise control of the trajectory or endpoint, anticipatory compensation for predictable external forces, or stability against unpredictable forces. The implemented scheme is an optimal feedback control law that defines how to integrate noisy and delayed sensory feedback signals with prior knowledge of the dynamical properties of the arm and efference copies of prior motor commands to generate an estimate of the current state of the system and the motor command to drive the arm from its current state to a desired goal state. The feedback gains that convert the current state estimate into motor commands are adjusted according to the goals and performance constraints of the task. Optimal feedback control does not make a strict serial separation between an open-loop movement planning stage and a subsequent movement execution stage. Instead, they are unified in the control circuitry and control laws. Optimal feedback control is a closed-loop process in which feedback is used continuously in real time to update the current-state estimate and to shape the motor command at all times prior to and during the movement. Stereotypical features of movements, including straight-line reaching trajectories with bell-shaped velocity profiles, simply emerge from the application of the optimal feedback control law, rather than being explicitly planned and controlled a priori by the central motor system.

Optimal feedback control theory likewise suggests that neural correlations with motor output parameters emerge in the activity of M1 neurons as a result of the interactions between feedforward and feedback signals that are required to implement the current control law. The observed neural response patterns and correlations with output parameters are a product of the control process, but may not provide a deep insight into the underlying computational mechanisms of an optimal feedback control circuit, such as the nature of the optimal control law and its associated cost functions, as they might for the more deterministic planning processes envisaged by force-control or position-control models.

Conclusion

Neurophysiological experiments have revealed neural correlates of many arm movement parameters, ranging from the spatial kinematics of hand path trajectories to muscle activation patterns. However, there is still no broad consensus on the role of the motor cortex in the control of voluntary movement. The answer to that question will depend as much on further theoretical insights

into the computational architecture of the motor system as on the design of the definitive neurophysiological experiment.

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