

Cortical mechanisms controlling limb movement

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Significant advances have been made this past year toward understanding the anatomy and physiology of motor cortical regions. New anatomical tracing techniques have elucidated intrinsic cortical connections as well as inter-areal connectivity. Magnetic stimulation of human cortex has provided new insights about the pathways mediating movements in humans. Neural recording studies in animals have further explored the behavioral variables that may be coded in activity of single units and populations. Recent approaches to neural network modeling offer some hope of synthesizing this wealth of detail into working simulations of networks that mediate motor behavior.

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Introduction

Recent studies of cortical mechanisms controlling limb movement tend to reflect one of two contrasting views of the functional organization of the motor system. The traditional view sees the motor system as a serial hierarchy of functionally distinct regions, whereas the alternative view stresses parallel distributed connectionistic processing. Indeed, most of the recent studies tend to further perpetuate, rather than resolve, this enduring dualism. Several reviews have addressed these issues, either explicitly or implicitly. A readable survey of the evidence that different cortical areas make distinguishable contributions to movement tends to favor the hierarchical model [1], i.e. that primary motor cortex is specialized for execution, whereas different premotor regions are preferentially involved in particular identifiable aspects of motor programming. Similarly, a review of cingulate cortical areas argues for further anatomic parcellation of motor regions into distinguishable and, presumably, functionally separable subsets [2].

In contrast, the connectionist view has been increasingly advanced in other reviews as a promising approach toward incorporating recent experimental results [3,4,5,6-7]. A broad-ranging discussion of controversial issues of motor control [4] has produced several target articles that have challenged the usefulness of traditional approaches to understanding motor mechanisms in terms of functionally distinct roles for anatomic sites or single cells. They have argued, for example, that "engineering-inspired, sequential/algorithmic models of motor processing" are incompatible with neural data [5], and that the analysis of firing patterns of single neurons is either totally hopeless [6] or a dubious exercise in reading selected tea leaves [7]. All three of these intentionally

provocative critiques have reached the same hopeful conclusion, that the inherent impasse of traditional approaches could be resolved by connectionist simulations of neural network operations.

This review summarizes a selection of recent studies relevant to cortical control of limb movement.

Cortical maps

Both the hierarchical and connectionist approaches must ultimately incorporate the known anatomical connectivity between cortical regions. The nature of cortical representation of movements has been perennially investigated by mapping the movements evoked by electrical stimulation of cortical sites. These studies have generated nearly as many motor maps as the number of mapping experiments, and recent results remain consistent with this rule. Although motor maps are usually similar in general location and broad features, their details can differ drastically. One likely reason for the diverse motor maps is the considerable variation between subjects, even when identical species and techniques are used [8,9,10,11]. Mapping the output sites for distal forelimb responses in anesthetized owl monkeys, Nudo *et al.* [8] found considerable differences between cortical maps in different animals; furthermore, even within the same individuals, statistical analysis revealed significant differences between the forelimb representation in the dominant and non-dominant hemispheres.

The precentral representation of fingers in the macaque motor cortex was recently 'mapped' with a novel technique based on the degree of single unit activity

Abbreviations

CM—corticomotoneuronal; HRP—horseradish peroxidase; IT—inferotemporal; LFP—local field potential; M1—primary motor cortex; PM—premotor cortex; PMd—dorsal PM; PMv—ventral PM; SMA—supplementary motor area; WGA—wheatgerm agglutinin.

recorded at different sites during relatively selective movements of the digits, rather than on the motor responses evoked by cortical stimulation [12]. Computer analysis of the spatial location of the cells with the strongest relation to each digit indicates a large overlap of representation of the digits in the precentral gyrus, favoring the idea of distributed representation.

The fact that the movements evoked by cortical stimulation can be modulated by sensory input has been demonstrated (again) in studies showing that the muscle responses evoked from rat motor cortex depend on the position of the limb [13]. The new interpretation of this phenomenon attributes the different output effects to a "reorganization of the cortical output map" [13]; alternatively, one could also imagine that the evoked responses could be changed by altered levels of excitability in the spinal cord, brain stem or other pathways mediating the output from cortical stimulus trains. As repetitive stimulation may stir up multiple pathways through temporal summation, it seems preferable to map output effects with single-pulse stimuli [14]; this approach has recently shown the existence of two forelimb output sites in the rat motor cortex [15].

Several studies have combined electrophysiological mapping, using cortical microstimulation, with anatomical tracing techniques to elucidate the connectivity between functionally identified motor cortex sites. Using localized injections of horseradish peroxidase (HRP) in macaques, Huntley and Jones [9] found profuse reciprocal connections between sites for finger, wrist and arm movement, but no connections between the face and forelimb movement regions. Similarly, in the cat, Keller [16] found intrinsic connections between forelimb sites, but negligible connectivity between forelimb and hindlimb or face sites. With localized injections of HRP and fluorescent tracers in primary motor cortex (M1) of owl monkeys, Stepniewska *et al.* [10*] found that intrinsic connections are strongest between closely related zones; this study also described differences in the architecture and connections between rostral and caudal M1 zones. A comparative study of local connectivity in different cortical regions found that the pattern and extent of the local spread of collateral fibers, as revealed by biocytin, have similar features across different cortical fields and species [17].

In addition to intra-areal connections, the connectivity between cortical fields has been further elucidated [2,18*,19–22]. Several recent studies have distinguished the distal and proximal forelimb representations in the macaque motor areas with regard to location and extrinsic connections [18*,23*]. The cortical inputs to distal and proximal forelimb sites in motor cortex (identified by microstimulation) were mapped with a double-labeling technique by Tokuno and Tanji [18*]. As illustrated in their summary diagram (Fig. 1), cortical neurons projecting to distal and proximal forelimb sites are largely separate in premotor cortex (PM), in primary and secondary somatosensory areas, and area 5, but are intermingled in supplementary motor area

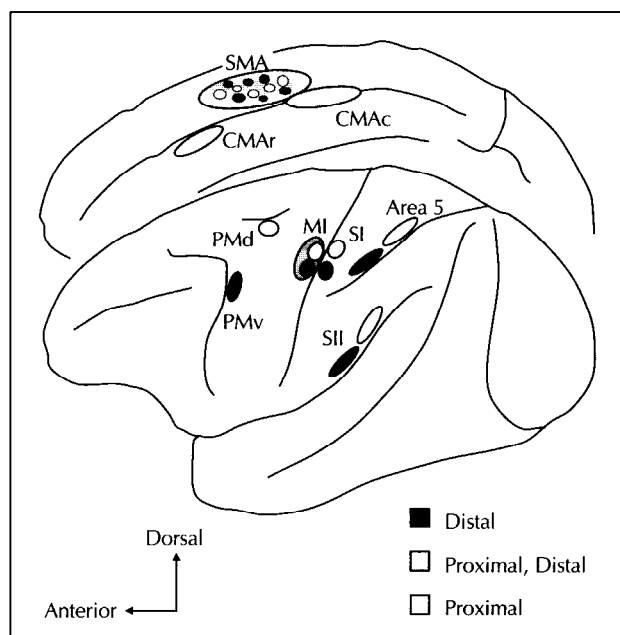


Fig. 1. Summary diagram of cortical areas containing neurons projecting to proximal and distal movement sites in the ipsilateral M1. The upper portion shows the medial surface as a mirror image; the lower portion is a lateral view. The filled, open and shaded areas indicate regions with labeled neurons that project to distal or proximal forelimb areas, or both. CMAc and CMAr: caudal and rostral cingulate motor areas; SI and SII: primary and secondary somatosensory cortex. Courtesy of Tokuno and Tanji [18*].

(SMA), cingulate motor areas, and adjacent precentral cortex. This was suggested to indicate that the latter regions may play a greater role in coordinating distal and proximal movements.

The distinction between distal and proximal representation was also a theme in anatomical studies of corticospinal projections. Using double retrograde labeling from upper and lower cervical segments, He *et al.* [23*] found that the pyramidal tract cells projecting to upper segments (containing primarily motoneurons of proximal muscles) tended to be separate from cells projecting to lower segments (with primarily distal motoneurons). Moreover, two foci of the latter group could be distinguished.

The terminal distributions of corticospinal neurons were mapped with anterograde transport of wheat-germ agglutinin (WGA)-HRP and compared for two New World primates [24]; both the cebus and squirrel monkeys had corticospinal terminations in the intermediate zone, but the cebus, which has greater ability to fractionate finger movement, had additional terminations among cervical motoneuron pools in the cervical and thoracic segments C8–T1.

Several new techniques have been developed for investigating functional motor pathways beyond the immediate projection sites labeled by conventional tracing methods. One technique employs *c-fos* induction as a functional marker for neurons activated by microstimulation of identified sites [25**]. Microstimulation of distal forelimb areas in rat motor cortex produces

c-fos expression in many regions; some of these were expected to be activated (e.g. cerebellum) and some were unexpected (e.g. subthalamus). Simultaneous use of anterograde tracers (PHA-L and biocytin) confirmed fiber projections to directly connected sites; curiously, some of the directly linked sites (e.g. ventrolateral nucleus of thalamus) did not show c-fos labeling.

A second method of labeling neurons in extended functional pathways utilizes transneuronal transport of markers. Alpha herpesviruses pass across synapses and replicate in synaptically linked populations of neurons, progressively increasing the signal with time [26]; this enhancement is an advantage over other transneuronal markers, such as WGA-HRP and tetanus toxin, which cross synapses in limited amounts. A recent description of the herpesviruses techniques summarizes the procedures and preliminary results of this approach [26].

Cortical stimulation in humans

Whereas much has been learned from animal experiments, the functional organization of corticospinal pathways has also been relentlessly probed in humans by transcranial magnetic stimulation of cortex. These studies have provided new insights into conduction times of corticospinal pathways [27–30], interactions of cortically evoked responses with voluntary movements [31,32*,33,34] and with peripherally evoked responses [35–38], as well as the development of the corticomotoneuronal (CM) projections in infant macaques [39].

Despite the large and uncertain extent of cortical excitation, magnetic stimulation has been used to distinguish differences in output sites in human cortex. Consistent with previous work, distal arm muscles had lower thresholds than proximal muscles for transcranially evoked electromyograph (EMG) responses, and could be activated from a larger and more laterally located cortical region [40,41]. Using the post-stimulus histograms of active single motor units to assess the nature of the cortically evoked postsynaptic potentials, Palmer and Ashby [42] showed that distal motoneurons receive excitatory inputs larger than biceps or triceps motoneurons; many of the latter are unaffected or are inhibited from cortex.

Magnetic stimulation has also been used to probe the changes in the excitability of corticospinal neurons [31,32*,35, 43]. Muscle stretch produces increases in cortical excitability, as revealed by increased responses of single motor units to appropriately timed magnetic stimulation [35]. Increases in cortical excitability preceding an active joint movement have been demonstrated by examining the enhanced effect on the H-reflex of weak magnetic stimuli that were subthreshold at rest [32*]. The output effects prior to movement can be attributed to increased excitability of corticospinal neurons. This technique revealed pre-movement increases in the facilitation of the H-reflex of agonist muscles as well as decreases in the H-reflex of antagonist

muscles. The time course of this pre-movement excitability increase and its effect on different muscles agree well with the response patterns and connectivity of CM cells in monkeys [14].

Neural coding

In addition to incorporating anatomical connectivity, theories of motor system organization must also explain observations of neuronal activity. The behavioral variables potentially coded in the activity of cortical units have been further explored, for both primary and associational motor areas. The most direct coding of muscle force would be expected from the primary motor cortex cells that affect muscles, as confirmed by post-spike facilitation of muscle activity in spike-triggered averages [14,44]. The contribution of these so-called CM cells to active force has been confirmed for the precision grip [44]; the activity of most CM cells exhibited the expected positive co-variation with active force, although a few showed an unexpected negative correlation with force, and with their target muscle activity. Most of these were 'ramp' CM cells whose activity increased during the static hold period, when activity of many motor units was decremending.

In cats, many motor cortex cells were found to modulate their activity with muscles during treadmill walking, and to show appropriately modified activity when the voluntary gait was altered during stepping over obstacles [45]. Most of these cells had definable receptive fields, which, interestingly, did not explain their responses during active movement, suggesting that central drive dominated over peripheral input during active walking.

In the primate many M1 neurons exhibit responses to peripheral stimulation. In a reaction-time task cued by ipsilateral cutaneous stimulation, many motor cortex neurons exhibit unexpected short-latency responses to the ipsilateral vibratory cues [46], confirming the diversity of cell types in motor cortex, extending from sensory- to movement-related neurons. To determine whether the responses of motor cortex cells to torque pulse perturbation of ongoing movement are influenced by input from the SMA, Schmidt *et al.* [47] cooled the SMA, but found relatively little effect on the evoked response of M1 neurons.

The role of PM cells in coding aspects of delayed responses has been further explored in several studies, with a particular effort toward distinguishing the functions of the dorsal and ventral components of this region (PMd and PMv, respectively). In a delayed response task in which instructions for the direction and amplitude of a subsequent movement were given separately by sequential cues, Kurata [48] found that all set-related PM neurons showed modulated activity after both instructional cues had been presented, but only a third responded differentially after the first instructional stimulus. Cells with set-related activity were

found predominantly in PMd, whereas movement-related cells were seen in both PMd and PMv. This suggests that PMd is related to motor preparation "by supporting neural programs necessary for an intended action, whereas PMv may be more specialized for execution of a visually guided movement" [48].

Other studies used clever behavioral paradigms to resolve the representation of sensory versus visuomotor signals in PM neurons [49–52]. Experiments designed to dissociate 'attentional' versus 'instructional' cues in three cortical areas (PMd, PMv and prefrontal cortex) used identical stimulus configurations for each type of cue [51,52]. The monkey fixated on a central stimulus while two visual cues were presented sequentially: a spatial-attentional mnemonic cue indicated where a subsequent motor-instructional/conditional cue would appear after a delay. This design allowed comparison of neural responses when identical stimuli, at the same retinocentric, craniocentric and allocentric spatial location, had different meanings. The experiment revealed that PM cells are more likely to code the motor significance of a stimulus than are prefrontal neurons [51]. Separate analysis of signal-, set- and movement-related activity revealed that a larger proportion of PMd neurons showed activity dependent on the action instructed by the stimulus, rather than the stimulus features per se [52].

Unit recordings in the medial hemisphere have revealed properties of SMA neurons [53], as well as cells rostral to SMA [54]. SMA neurons were found to be involved in early stages of externally cued reaching movements, and other cells fired only during self-generated movements [54].

Population coding

Studies of the coding of limb movements in populations of cortical neurons were recently reviewed [3*,55], and the methods extrapolated to analysis of cognitive processes underlying motor activity [55]. The latter paper presented evidence that cortical neurons with similar directional preference had excitatory synaptic connections, whereas those with opposite preferences had inhibitory connections. However, the unconventional technique used to estimate the synaptic 'interactions' was strongly affected by response similarity, as demonstrated by simulations [56].

Several recent papers have provided further information about population coding. Fortier *et al.* [57] compared the properties of cells in motor cortex and cerebellum to whole-arm reaching movements in eight planar directions. Compared with cerebellar neurons, the motor cortex cells were more strongly related to maintenance of different arm postures; i.e. they more often showed different sustained discharge rates, and a greater proportion showed reciprocal changes relative to opposite movement directions from the center hold; moreover, the motor cortex neurons exhibited

less trial-to-trial variation in firing rates than cerebellar neurons. A similar contrast was found for thalamic cells receiving cerebellar input, which fired phasically and bidirectionally more often than motor cortex neurons [58].

Schwartz [59] showed that the directional properties of a population of selected motor cortex neurons (responsive to passive shoulder and/or elbow movements and whose activity varied as a cosine function of direction) could be used to predict responses in a movement different from the center-out trajectories used to determine their spatial tuning. These cells generated a population vector that matched the tracing of sinusoidal trajectories with the finger, and the increments in the traced trajectory were predicted by a population vector that preceded the trajectory increments by about 120 ms.

The relationship of motor cortex neurons to changes in force was re-examined in a task requiring ballistic movements in different directions [60]. These behavioral conditions favor the finding of relations to changes in force, which were duly emphasized in the paper. A newcomer to the field could well be baffled by seemingly contradictory claims that motor cortex neurons code direction of movement [55,57,59], active force [14,44], and now, changes in force [60]; the apparent discrepancies can be resolved by recognizing the differences in experimental conditions of each study, as well as the interpretative emphasis of the experimenters.

Cortical oscillations

In addition to the modulated firing rates of cortical neurons during movement, there appears to be another, orthogonal, mode of neural activity in sensorimotor cortex. As found in visual areas [61], local field potentials (LFPs), as well as many neurons in motor and somatosensory cortex of awake monkeys, show intermittent episodes of oscillatory activity [62–64]. These oscillations occur in phase over remarkably large regions, indicating that the activity of widespread populations of neurons becomes transiently synchronized. Coherent oscillations have been documented between pre- and post-central cortex [62], M1 and PM [63], and bilaterally, between hemispheres [64]. Although synchronous oscillatory activity can be robust and widespread, its functions, if any, remain to be proven. During free limb movements, the oscillations increase during tasks that require attention to fine sensorimotor control, such as retrieving raisins from unseen locations [62,64]. In human subjects the epicortical electrocorticogram can show high frequency 40 Hz oscillations at specific sites during a two-dimensional video tracking task [64]. In a conditioned delay task, LFP oscillations also regularly precede movement, becoming desynchronized with movement onset [63]. These observations are consistent with a role of sensorimotor cortex oscillations in facilitating associations between

large populations of cells, analogous to the binding function proposed for visual cortex neurons [61]. The occurrence of oscillatory episodes and the strength of the correlations between LFPs at different sites do not appear, however, to be closely linked to behaviors that involve neurons at the two sites [64]. Cortical oscillations may also be concomitant with increased attention or arousal, and may either be an epiphenomenon of increased excitability or used to recruit larger groups of neurons into associated activity.

Neural modeling

The expanding wealth of experimental detail about anatomical connections and neural activity during movement must ultimately be synthesized into plausible models of motor system function that consist of more than descriptive conceptual schemes. The proof that a particular model actually works is provided by the demonstration of its efficacy through simulation. Simulations with dynamic neural networks can provide important insights into computation in distributed populations of interconnected neural elements [65,66*,67,68*].

Several papers have modelled the processes underlying transformation of vector representations from visual to motor coordinates. A relatively abstract model described circuitry that could combine visual vectors indicating target location with proprioceptive vectors representing limb position to calculate movement vectors indicating direction to move [69]. The mediating 'units' represented cortical modules with sophisticated computational capacities. How the neurons comprising the column modules performed their intrinsic operations remains largely unanswered. A more explicit neural network model was explored by Kettner *et al.* [70] who simulated the transform of sensory to motor vectors with a feedforward network of sigmoidal units, using backpropagation to derive the connections. The hidden units had spatial tuning functions resembling those encountered in cortical neurons, and the number of cells in the intermediate layers clearly affected the variety of representations. The steady-state activity in directionally tuned cells can be sustained with connections between units that are directly proportional to the similarity in their directional preference [55].

Perhaps one of the most exciting demonstrations of how dynamic recurrent networks can elucidate neural mechanisms involves simulations of short-term memory [68*]. Networks can be trained, purely on the basis of examples, to retain arbitrary analog input values that occur at the times of intermittent gating pulses. The mediating units have distinctive discharge patterns during the input and the delay period that resemble the patterns of cortical neurons recorded in monkeys performing analogous short-term memory tasks. Distinct corresponding classes of cortical cells and hidden units can be identified [68*]. The function of the

cells in mediating input and the retention phase of the sample-and-hold operation can be clarified by reducing the networks to their minimal configuration [66]. Unlike the situation in monkeys, in which the function of cortical cells remains a matter of speculation in the absence of information about their connectivity, the function of the network units can be explicitly analyzed, as their contribution to the network operations is clear from their connections and activity.

Besides providing complete network solutions simulating normal behavior, neural network models can also be readily manipulated; for example, investigators can create lesions to determine whether the absence of certain units leads to a functional deficit [66*]. Such lesions can even be used to mimic certain clinical situations [71].

Concluding comments

These recent studies of the connectivity and activity of motor cortex neurons provide further support for both hierarchical and connectionist views of the organization of motor systems. The separate output areas identified by microstimulation are heavily interconnected, yet with some functionally significant restrictions. The activity of cortical cells has been shown to correlate with particular response features; yet neurons with similar properties are widely distributed. Our best hope of synthesizing the inherently selective anatomical and physiological data about portions of the nervous system may come from neural network modeling. By incorporating known connections and activation patterns into simulations of behavioral performance, neural networks can provide a valuable bridge between cellular and systems levels, and significantly elucidate the neural mechanisms of behavior.

Acknowledgements

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3. KALASKA JF, CRAMMOND DJ: Cerebral Cortical Mechanisms of Reaching Movements. *Science* 1992, 255:1517-1523.

A re-evaluation of hierarchical models of motor system organization in light of newer results favoring connectionist explanations. A diplomatic attempt to straddle both views.

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A lively discussion of contemporary issues of motor control, from the inaugural Portland "Controversies in Neuroscience" meeting. Target articles deliberately designed to take provocative stands succeeded in evoking responses from a wide range of respondents. Over a hundred commentators contributed to spirited discussions of the issues and philosophy of motor control research.

5. ALEXANDER GE, DELONG MR, CRUTCHER MD: Do Cortical and Basal Ganglionic Motor Areas Use "Motor Programs" to Control Movement? *Behav Brain Sci* 1992, 15:656-665.

This articulate analysis argues that "prevailing engineering-inspired theories of motor control based on sequential/algorithmic or motor programming models" are incompatible with much current anatomical and physiological information. Recent neural recordings show that information is represented in parallel in distributed networks, which are more likely to be elucidated with connectionist models.

6. ROBINSON DA: Implications of Neural Networks For How We Think About Brain Function. *Behav Brain Sci* 1992, 15:644-655.

The new testament of a prior apostle of engineering, black-box models of motor systems, now converted to the connectionist creed by revelations from neural network models. Simulations of oculomotor operations reveal hidden units with a complex variety of responses (like biological networks), including 'rogue' cells whose activity appears counterintuitive. The take-home lesson for neurophysiologists: "trying to explain how any real neural network works on a cell-by-cell, reductionist basis is futile".

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A critique of the experimental strategy of inferring functional representation and mechanisms from the response patterns of neurons recorded in behaving animals. The common selection bias in chronic unit recording experiments favors analysis of cells with interpretable relations to the trained task and ignores cells with more complex relations and unmodulated neurons. Experiments in which both the activity and connectivity of cells is known show that all three groups of neurons can and do contribute to motor output. These experiments include unit recordings in which the connectivity of the recorded cells is determined by cross-correlation, as well as dynamic neural network models that simulate behavioral responses. The proposed solution to understanding network mechanisms is modeling, which can simulate behavior while incorporating many constraints on connectivity and activity.

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Cortical and subcortical neurons projecting to distal and proximal sites in M1 were labeled by dual injections of retrograde tracers. The injection sites were identified by intracortical microstimulation. Neurons projecting to the distal and proximal precentral sites were largely separate in several regions: PM, primary and secondary somatosensory cortex, area 5 and thalamus. In contrast, the labeled neurons were intermingled in SMA, cingulate cortex, claustrum and the basal nucleus of Meynert; this intermingling suggests that the latter regions are more probably involved in coordinating distal and proximal movements.

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ments (corresponding to proximal and distal musculature) tended to overlap in both M1 and PMd, although the densest projections arose from separable sites. PMv cells projected to upper cervical segments and below T7. Unexpectedly, two M1 sites project to lower cervical segments, presumably affecting distal muscles.

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