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Motor maps and the cortical control of movement

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The brain's cortical maps serve as a macroscopic framework upon which additional levels of detail can be overlaid. Unlike sensory maps generated by measuring the brain's responses to incoming stimuli, motor maps are made by directly stimulating the brain itself. To understand the significance of motor maps and the functions they represent, it is necessary to consider the relationship between the natural operation of the motor system and the pattern of activity evoked in it by artificial stimulation. We review recent findings from the study of the cortical motor system and new insights into the control of movement based on its mapping within cortical space.

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Introduction

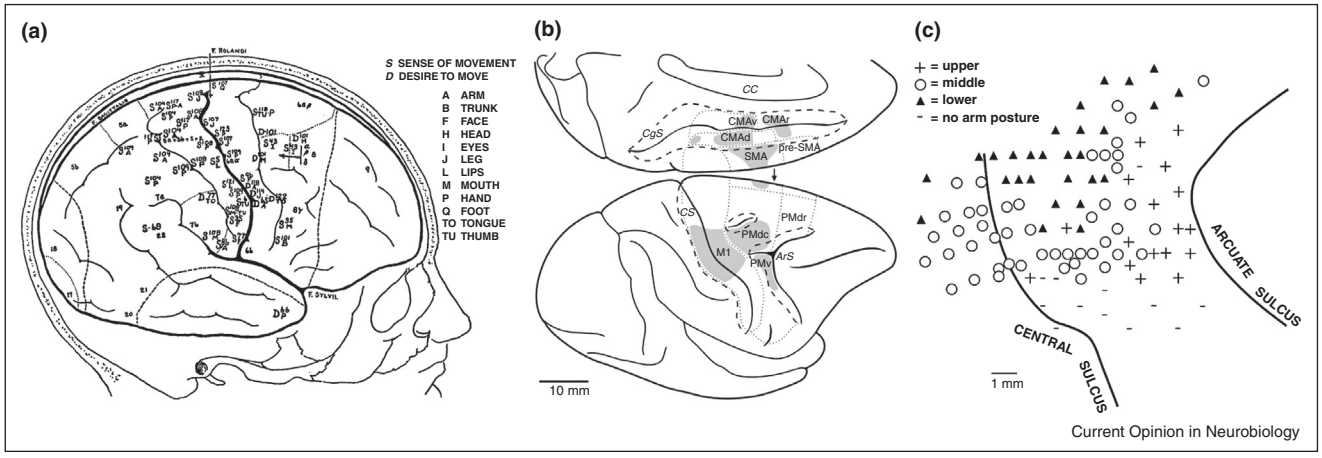
Mapping is a fundamental part of any systematic investigation of the unknown, yet the map of the brain still contains swaths of *terra incognita*. In addition to gross anatomical or cytoarchitectonic parcellation of the brain, physiological details must be added in the form of functionally defined brain regions. Many cortical areas can be surveyed by recording brain activity evoked by specific stimuli delivered to the sensory periphery, but motor maps are unique in the sense that they are created by directly stimulating the brain itself. Meaningful interpretation of a motor map therefore requires an understanding of both the natural flow of activity through the cortical motor system and its reverberation through the same network upon artificial stimulation. Here, we review recent studies of naturally occurring and stimulus-evoked activity in motor cortex in an attempt to strengthen the link between movements and their representation in cortex. The significance of maps for motor control and of their plasticity for recovery from injury is examined. Finally, we discuss new light-based methods for mapping motor cortex.

What form do motor maps take and what purpose do they serve?

Traditionally, motor maps have been structured according to the correspondence between a cortical point and the muscles that are activated by its stimulation. Early experiments with cortical stimulation in human surgical patients revealed a somatotopic organization of motor cortex, giving rise to the enduring concept of the motor homunculus (Figure 1) [1]. This view progressed to include multiple premotor regions in the cortices of non-human primates [2,3], many of which project directly to the spinal cord [4] (Figure 1). Parameters of movement have also been used as an organizing principle for cortical mapping. In an influential series of experiments in monkeys, the firing rates of individual neurons in motor cortex were found to be related to the direction of forelimb movement by a sinusoidal function, termed cosine tuning [5]. Cells fired most vigorously during forelimb movements in a particular preferred direction; these directions can be weighted by firing rate and summed to produce a population vector that predicts movement direction [6]. This finding has led to the development of brain machine interfaces capable of extracting information from neuronal activity to control prosthetic [7,8] or paralyzed limbs [9]. Complementary experimentation with prolonged electrical stimulation revealed a macroscopic organization of movement categories or postures in motor cortex [10,11]. Similar movement maps have since been described in humans [12,13] and rodents [14–16].

Although the activity of motor cortex appears to be related to movement direction, this could also reflect the contribution of limb biomechanics to a system primarily concerned with the control of the musculature [17••]. For example, motor maps can be interpreted as representing movement endpoints or postures [18] or as the activation of muscle synergies independent of the initial configuration of the limb [19••]. Attempts to identify the movement-related variables encoded by the firing of motor cortex neurons have revealed a bewildering complexity of neuronal tuning [20]. The influence of externally applied loads or initial joint angle varies among neurons [11,21], with multiple forms of tuning reflected at the population level [22]. This complexity may result from a motor control strategy that employs sensory and proprioceptive feedback to optimize movements toward a behavioral goal despite variability and noise in both sensory input and motor output [20,23,24]. The observation that movements evoked by stimulation of a given

Figure 1



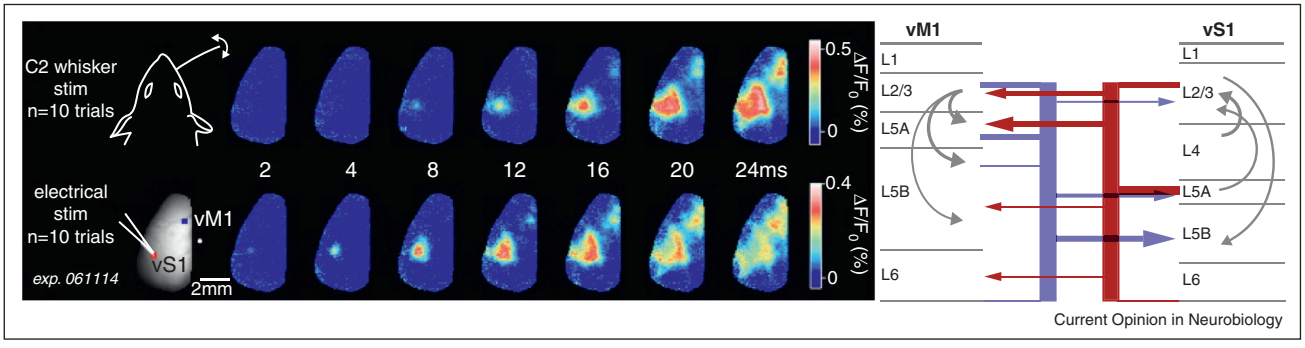
Movement maps in motor cortex. **(a)**, composite map created from data collected in human surgical patients [1]. **(b)** Multiple motor regions in macaque cortex, with areas containing retrogradely labeled corticospinal neurons marked in gray (modified from [4]). **(c)** Magnified view of macaque motor cortex labeled according to the endpoint of arm movement evoked by electrical stimulation [10]. Abbreviations: *ArS*, arcuate sulcus; *CC*, corpus callosum; *CgS*, cingulate sulcus; *CS*, central sulcus; M1, motor cortex; SMA, supplementary motor area; PM, premotor cortex (lower case suffixes denote dorsal, rostral, and/or ventral subregions), CMA, cingulate motor area.

cortical point tend to converge toward a consistent endpoint or posture rather than following an invariant trajectory could be taken as support for this model of cortical motor function.

An additional function of the cortical motor system is the integration of motor acts with sensory feedback. In rodents especially, it may be more correct to speak of the sensorimotor system as a whole given the degree of overlap between sensory and motor representations of the limbs [25,26]. The distinction between movement and sensation is also blurred in cases such as the rodent vibrissal system, where the whiskers must be moved to scan the environment. Though non-overlapping regions of vibrissal sensory and motor cortex exist in mice these areas are closely integrated (Figure 2). Neuronal firing in whisker motor cortex encodes the angular position of vibrissae [27] and modulates somatosensory cortical activity [28], whereas stimulation of sensory cortex drives whisker movements via a direct projection to the brainstem [15]. Sensorimotor integration extends beyond the somatosensory system, with motor activity modulating the function of visual cortex [29,30•].

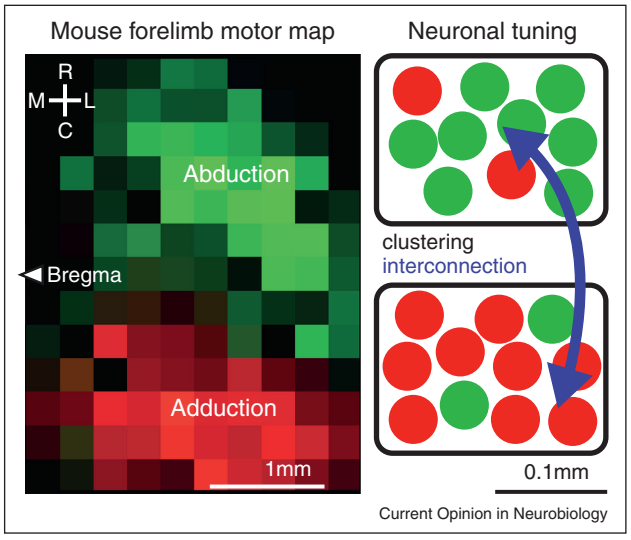
More fundamentally, one can ask why topographically organized maps should exist at all, rather than a more stochastic (''salt and pepper'') arrangement of neurons. Explanations for clustering include the reduced axonal lengths needed to link preferentially interconnected neurons with similar response properties [31]. Another

Figure 2



Natural and stimulus-evoked patterns of dynamic cortical activity. At left, voltage-sensitive dye imaging data illustrating the flow of activity through cortex following tactile stimulation (top) and electrical microstimulation of sensory cortex [52]. The flow of natural or evoked activity between whisker sensory (vS1, red dot at lower left) and motor cortex (vM1, blue dot) depends on the connectivity between these regions (right) [49].

Figure 3



Properties of motor cortex underlying motor map structure. Motor maps (e.g. the light-based movement map at left [16]) are products of the cortical circuitry and the manner in which it responds to artificial stimulation. Macroscopic subdivisions of motor maps into regions such as the forelimb abduction and adduction areas (green and red regions of map at left) likely arise from microscopic clustering of neuronal properties. The green and red circles represent neurons with different functional properties clustered within the black rectangles. The anatomical substrate of motor maps also includes long-range connections (bidirectional blue arrow) that link distant cortical regions.

possible determinant of map structure stems from the increased connectivity observed between clonally related cells in cortex [32].

What features of motor cortex circuitry give rise to movement maps?

Emerging evidence from imaging experiments has contributed to our understanding of the function of motor cortex at the level of individual neurons (schematized in Figure 3). Although neuronal response types appear to be intermingled in motor cortex as in rodent visual cortex [33], calcium imaging of L2/3 neurons in small fields of mouse motor cortex (200 μm) has revealed a correlation between the proximity of a pair of neurons and their activity profiles during motor behavior (e.g. running vs. grooming) [34]. This clustering exists at fine scales (~100μm), exhibits temporal specificity for distinct phases of motor acts such as lever pulling [35•], and strengthens during learning [36]. Furthermore, the activity of neurons situated within such clusters better predicts ongoing motor behavior than more dispersed cells [35•]. Cortical microstimulation, particularly if restricted to a minimal volume of tissue [37], could potentially recruit small clusters of neurons that share synaptic inputs, exhibit coactivity and possess similar tuning.

The extent to which evoked activity can be compared to the natural state during self-initiated movement further depends on its downstream spread. The motor cortex is an interconnected network, bound together by axon collaterals that form boutons along their full lengths of up to 7 mm in the cat [38]. The cortical points linked by these collaterals can be functionally coupled through the release of inhibition [39], and upon co-activation their evoked motor activity sums linearly [40]. Consequently, motor maps do not represent the motor output of an array of independently activated cortical points. Rather, stimulation anywhere in cortex likely triggers a cascade of activation through horizontal interconnections, potentially recruiting additional output from distant locations. The propagation of this activity is thought to be channeled through excitatory cortical circuits and shaped by inhibition [41].

The considerable advances in brain-machine interface research have been a boon to our understanding of natural dynamic activity in the cortical motor system [42]. Longitudinal cortical electrophysiological data have been collected from animals engaged in the learning and execution of a variety of motor acts [43,44]. These recordings are typically performed using multi-site electrode arrays, permitting the spatiotemporal progression of activity through motor cortex to be recorded [45•]. On the basis of these experiments, it has been proposed that cortical activity follows a dynamic trajectory through neural space during movement preparation and execution [46••,47]. It is not clear from the electrophysiological data how this trajectory through abstract space corresponds with the flow of activity through physical circuits in the brain, but the latter can be hypothesized from our increasingly detailed knowledge of connectivity within and between cortical areas [48,49]. A question of primary concern for physiologists employing brain stimulation is the extent to which the brain activity produced by this artificial stimulus resembles the natural pattern of activity during self-initiated movement.

How does cortical stimulation drive complex movements?

The effects of artificial stimulation on brain activity are increasingly well documented. Pharmacological disinhibition in a small region (~800 μm in diameter) of cat motor cortex creates bursts of neural activity that propagate within an area of ~7 mm^2 and are not significantly affected by thalamocortical transection [50••]. Optogenetic stimulation of as few as 60 layer 5 cortical neurons in mice can initiate waves of activity that spread through both cortico-cortical and cortico-thalamic pathways [51]. These results suggest that intracortically spreading activity could potentially recruit large cortical areas for the integrated control of multi-jointed movements. Voltage-sensitive dye imaging has revealed that this activity propagates preferentially between interconnected areas

(Figure 3). For example, electrical stimulation of somatosensory cortex triggers a pattern of dynamic activity similar to that observed after sensory stimulation of the corresponding body part [52,53•]. This spread of activity is likely mediated by connections that selectively innervate cortical domains and even exhibit specificity for the functional profile of the downstream target [54•]. Magnetic resonance imaging following optogenetic stimulation has illuminated functional connectivity on a global scale, albeit with decreased spatial and temporal resolution [55,56].

Cortical stimulation has been hypothesized to recruit the circuitry of motor cortex to produce naturalistic complex movements [11]. It is surprising that these movements can be evoked with relatively simple stimulus trains given that the simultaneous activation of many neurons is unlikely to replicate the temporal structure of natural activity [57,58]. Indeed, electrical stimulation may override and replace ongoing natural activity by antidromically obliterating action potentials [59••]. In many ways, however, stimulus-evoked movements do resemble natural movements. The expression of these movements requires the intact function of the intracortical circuitry and can be disrupted by the application of glutamate or GABA receptor antagonists [16]. Complex movements of the forelimb are only evoked by pulse trains lasting hundreds of ms [10,14,16,60,61], corresponding to the typical duration of a reach. In monkeys, these prolonged pulse trains recruit muscle synergies of the hand that closely resemble those recorded during complex natural grasping movements [19••].

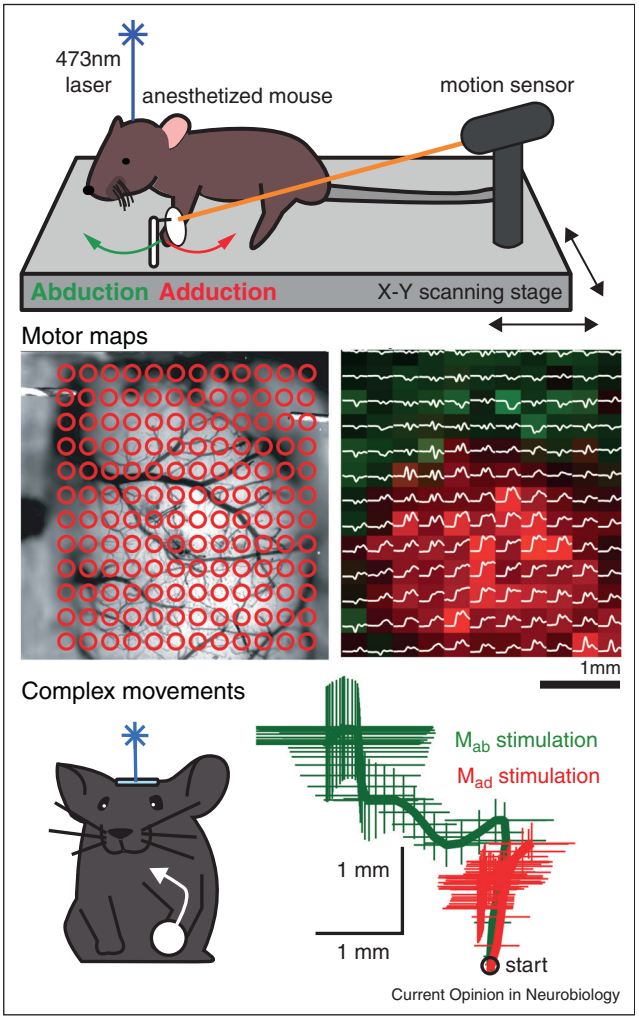
Plasticity of movement maps

Motor maps have provided some of the most convincing demonstrations of the brain's ability to reorganize during the acquisition of new skills [62,63] or after injury [64–69]. Map plasticity is associated with synaptic alterations [70] and spine turnover [71–75] in addition to remodeling of axonal processes [76,77]. Cortical stimulation has been investigated as a means of enhancing motor learning and rehabilitation after injury, and appears to be most effective when combined with motor training [78–82]. It therefore seems reasonable to hypothesize that nonspecific stimulation, if applied in conjunction with spontaneous, goal-directed activity in the motor system, may be able to augment cortical plasticity and improve recovery. Further research in this area has the potential to both deepen our understanding of the cortical motor system and to optimize rehabilitative strategies [83].

Technical advances in motor mapping

The ever-expanding suite of optogenetic tools has enabled the use of light-based stimulation for motor mapping (Figure 4) [25]. Light-based mapping is rapid and minimally invasive, permitting repeated mapping over time scales ranging from minutes to months

Figure 4



Light-based motor mapping. Top: method for light-based mapping in Channelrhodopsin-2 transgenic mice [16,25]. Anesthetized mice are placed on a scanning stage and their motor cortex is stimulated with 10ms pulses from a 473 nm laser (blue asterisk) while evoked movements of the contralateral forelimb are recorded using a laser motion sensor. Middle: stimulation is targeted to an array of sites (left) to generate a pixel-based map (right) where movement amplitude is indicated by pixel brightness and movement direction by color (red for adduction, green for abduction). The map is overlaid with movement sensor recordings in white (mean of three repetitions). Bottom: after generating a motor map the centers of the abduction and adduction motor regions can be targeted for stimulation (500 ms pulse train) while unrestrained movement trajectories are recorded with a video camera (left). Trajectories at right represent the mean of 16 mice, error bars are SEM.

[16,25,84]. This has facilitated comparisons of map organization immediately before and after application of pharmacological agents [16] and enabled longitudinal studies in animal models that would not otherwise be possible [69]. Finally, light-based mapping can repeatedly sample hundreds of uniformly distributed cortical sites in a randomized order to minimize the confounding temporal effects of anesthesia [85] and cortical plasticity

[86]. As with any technique, the advantages of light-based stimulation are balanced by its limitations. Scattering degrades the spatial resolution of light-based motor mapping [87]. The cellular consequences of long-term expression of high levels of membrane protein must also be considered [88]. To date, most optogenetic experiments have been performed in rodents, though research in primates holds promise [89]. Many of the greatest advantages of optogenetics for motor mapping have yet to be realized, however, and will likely stem from the ability to activate, inhibit, or modulate specific classes of neurons. For example, Thy-1 transgenic mice [90] express ChR2 predominantly in layer 5 cortical neurons, meaning that these output neurons can be stimulated relatively selectively [25,36,84]. Alternate expression methods can target neurons according to their transmitter type, cortical layer [91,92], or even their connectivity [93••,94].

Conclusion

Decades of experimentation in the motor cortex have contributed successive layers of detail to motor maps. This increasing complexity and sophistication is a reflection of the cortical circuitry and the functions that it serves. In order to appreciate the significance of a motor map, however, it is necessary to understand the physiological consequences of the artificial stimulation used to produce it. The fidelity of motor maps depends on the similarity between natural and stimulus-evoked cortical activity. As additional data about static connectivity and the dynamic flow of activity through cortical circuits are collected, this comparison will continue to be reassessed and the meaning of motor maps reevaluated.

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