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Coding of movements in the motor cortex

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The issue of coding of movement in the motor cortex has recently acquired special significance due to its fundamental importance in neuroprosthetic applications. The challenge of controlling a prosthetic arm by processed motor cortical activity has opened a new era of research in applied medicine but has also provided an 'acid test' for hypotheses regarding coding of movement in the motor cortex. The successful decoding of movement information from the activity of motor cortical cells using their directional tuning and population coding has propelled successful neuroprosthetic applications and, at the same time, asserted the utility of those early discoveries, dating back to the early 1980s [1,2].

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Introduction

There is little doubt that motor cortex controls movements. Hughlings Jackson put it elegantly in his paper titled 'On some implications of dissolution of the nervous system' in 1882, as follows: 'Nervous centres represent movement, not muscles. From negative lesions of motor centres there is not paralysis of muscles, but loss of movements.' [3•]. The current state of affairs is that we are still working on the details. As Jackson referred to them, movements are coordinated motions about joints, brought about by changing muscle contractions and producing motion of limb endpoints (hands, feet, etc.) over space and time. Jackson's essential point was that the motor cortex is involved in this *coordinated* motion, not just haphazard muscle contractions. Although these issues have been debated as the famous 'movement vs. muscle' controversy [4], there is ample evidence now that descending motor cortical control is fairly distributed across brain areas, spinal centers, principal neurons and interneurons, neural networks, etc. [5••]. In fact, there is compelling evidence for the involvement of motor cortex in cognitive operations as well, beyond simple motor control [6,7,8]. Thus, it is important to keep in mind that the role of motor cortex in the control of movement is only one aspect of its overall function. It would be fair to say that motor cortex is involved in motor 'stuff', be it real movement, imagined movement, or motor cognition.

Conceptual limitations of the experimental design

The knowledge gained by a study is delimited by the breadth and depth of the question, the experimental design and the methods used. The traditional way by which the role of motor cortex in the control of movement was investigated was to conduct experiments where a motor variable was varied in a controlled way while motor cortical activity was recorded simultaneously. To analyze the data, linear regression has been employed as the venerable statistical method to discover and quantify relations between motor cortical activity and motor variables. A major limitation of this approach has been the necessary restriction of the motor variables studied, due to conceptual and technical limitations. For example, a conceptual limitation up to 1980 was the implicit assumption that motor cortex is involved only in intrinsic motor control, that is, control of muscles or movements about mostly single joints. Practically all of the tasks used were about a single joint, and, when joints allowed multidimensional motions (e.g. wrist, shoulder or multiple joints), the experimental design typically restricted motion to one dimension (e.g. push–pull or side-to-side at the wrist). In the extreme case, in the study by Murphy and collaborators [9], data from a truly multidimensional movement experiment were interpreted within a then fashionable restrictive context, with the resulting loss of the true and precious information. Specifically, 3-D reaching movements were deconstructed to constituent compound joint movements, and motor cortical activity was analyzed with respect to joint motions or muscle activity, with essentially negative results, that is, lack of consistent association between neural activity and joint movements or muscle activity [9]. In that era, referring motor cortical activity to movement of the hand in extrapersonal space, as we implemented with the center → out task [1], was a conceptual leap. Thirty-four years later, the center → out task has now become commonplace but the conceptual leap seems to have been forgotten or overlooked.

We are now faced with a similar situation. All along, it has been assumed that motor cortical activity relates only to a specific body part, and we have typically differentiated between cell activity related to arm or hand movements. We accounted for coordinated arm-and-hand movements by referring neural events to a coordination at the population level, namely between arm-related [2,10] and hand-related cells [11]. Existing, known connectivity within motor cortex and among cortical and subcortical motor structures was invoked to model coordinated activity among body parts. Now, neuroprosthetics is adding another dimension to this outlook, namely that individual motor cortical cells may well relate to multiple aspects of movements, encompassing coordinated arm-and-hand functions. We discuss these issues separately below.

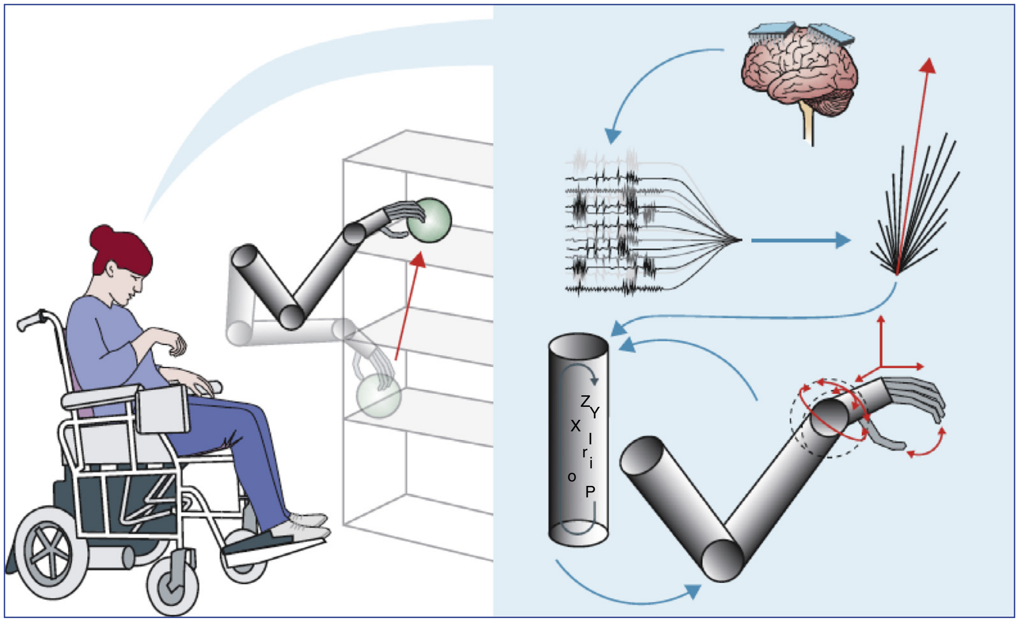
Motor cortical coding of reaching

This issue has been now clarified. The activity of single cells in the motor cortex varies in an orderly fashion with reaching movement parameters [1,12,13,14,15]. The overall activity is tuned to the direction of movement in space [1,12], a finding also confirmed in human subjects using fMRI [16•]. As put succinctly by Ebner and colleagues, movement parameters are 'multiplexed' in motor cortical activity [17]. This fact, while illuminating, also begs the question of how motor cortical activity could uniquely encode an evolving reaching movement. This problem was solved by applying a population code [2,10]. This code was initially applied to average motor cortical activity and yielded accurate prediction of the direction of movement [9,10]. Subsequently, it was used to derive, for the first time, a neural representation predictive of the upcoming movement trajectory [18]. This was followed by the derivation of a highly accurate neural population signal of continuous drawing movements in 3-D space [19,20]. These studies provided a translational 'handle' and effectively opened the door for the motor cortical control of the movement of a prosthetic arm. Initial successful application in monkeys [21,22,23] was followed by full-fledged application in humans [24,25••]. Figure 1 (from [26•]) illustrates nicely the current, state-of-the-art setup for motor cortical neuroprosthetics [24].

Motor cortical coding of grasping and individuated finger movements

Grasping is a common motor act closely associated with reaching, hence the expression 'reach-and-grasp'. In 2002, Ebner and colleagues proposed that motor cortex may control the hand as a unit [27], a hypothesis that was investigated rigorously later [28] using grasping of various objects of different sizes, volumes and shapes (Figure 2). The activity of the large majority of cells in the motor

Figure 1



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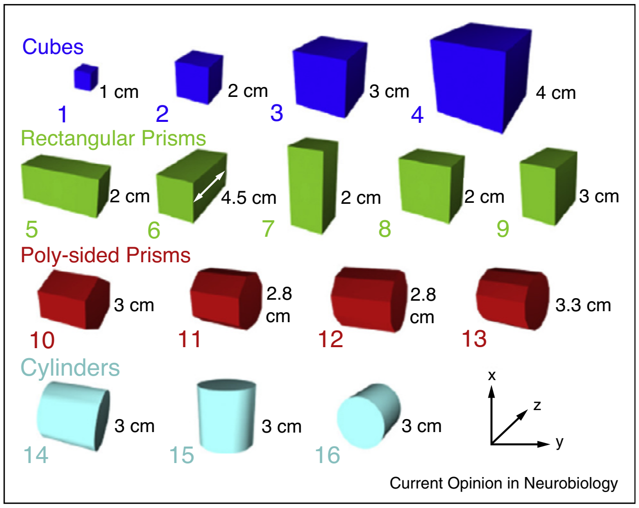
A tetraplegic woman is sitting in her wheelchair with an anthropomorphic prosthetic arm on her side. Two silicon-substrate microelectrode arrays surgically implanted in the motor cortex allow recordings of ensemble neuronal activity. A population vector algorithm translates brain waves into intended movement commands. This brain-derived information is conveyed to a shared controller that integrates the participant's intent, robotic position feedback, and task-dependent constraints. Using this bioinspired brain–machine interface, the paralysed woman could manipulate objects of various shapes and sizes in a three-dimensional workspace. Figure and legend from [26•].

Figure 2



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Objects used to study motor cortical relations to grasp [26•]. Four object classes (cubes, rectangular prisms, poly-sided prisms, and cylinders) were presented with the *x*–*y* plane parallel to the frontal plane of the monkey. Grasp dimensions measured along the *z*-axis (e.g., as shown by the white line segment on object 6) were 1, 2, 2.8, 3, 3.3, 4, or 4.5 cm. The cubes had volumes of 1, 8, 27, and 64 cm^3, the rectangular solids had a volume of 18 cm^3 (3 were 4.5 × 2 × 2 cm and 2 were 2 × 3 × 3 cm), and the poly-sided prisms and cylinders were 3 × 3 cm (length × diameter). The poly-sided prisms had 6, 8, 10, or 12 sides.
Adapted from Fig. 1 in [28].

cortex was modulated by the ‘grasp dimension’, that is, the grasp width of the object. Other aspects of the object (e.g. volume or class) did not provide additional information on the parameters of object shape represented in these neurons. The correlation to grasp dimension became stronger as the hand came nearer to the object.

In grasping, finger movements are coordinated to produce an aperture appropriate for the object to be grasped. In contrast, a finger can be moved separately, in what is called ‘individuated’ movement. The relations of motor cortical cell activity to such individuated finger movements have been investigated extensively by Schieber and his colleagues [29]. The main finding of these studies was that the activity of single motor cortical cells typically relates to the movement of more than one finger [29]. In that study, the finger movement space comprised flexion/extension of five fingers and the wrist. Quantitative aspects of cell activity were explored using this finger-space framework; it was found that 75% of the cells were tuned in that space [11]. Moreover, a population vector analysis yielded a very good prediction of the direction of finger movement in that space, within 30 deg of the actual movement ($P < 10^{-5}$). The prediction was even more accurate (within 16 deg of the actual movement) when the optimal linear estimator [30] was used. However, the better predictions obtained from this and similar subsequent analyses [31] are due to the optimization of the cell weights contributing to the calculation of the population vector, that is, the adjustment of the weighted cell contribution to minimize the prediction error. This gives, in a way, the best possible outcome. In contrast, the original population vector calculation reflects the reality of the experiment and not its best possible outcome obtained by the back-propagated error-minimization procedure.

Motor cortical coding of reach-and-grasp

Up to now, neural activity at the single cell level had been investigated under separate paradigms for reach or grasp, as discussed above. Information concerning both reach and grasp was obtained using mixed recording from various sites and kinds of neural signals [32,33]. The breakthrough of recording from the human motor cortex for prosthetic control has served well the objective to direct mentally the arm in space and position of the robotic hand where the patient desires, thus closing the loop and lending decisive support to the original idea that motor cortex controls movement in space [1,2]. This new setup made it possible to test the hypothesis that the activity of single motor cortical cells could relate to *both* reaching and grasping. This is of special importance to humans, who possess exquisite control of the hand. This hypothesis was tested rigorously in a human subject who mentally operated a fairly sophisticated 10-degree of freedom anthropomorphic arm [25••]. Reaching movement parameters as well as a number of hand shape parameters were entered into the regression model as independent variables, with single cell motor cortical activity as the dependent variable. Significant relations were found for all parameters, clearly documenting the participation of motor cortical cells in the simultaneous control of reach and grasp.

Neural substrates

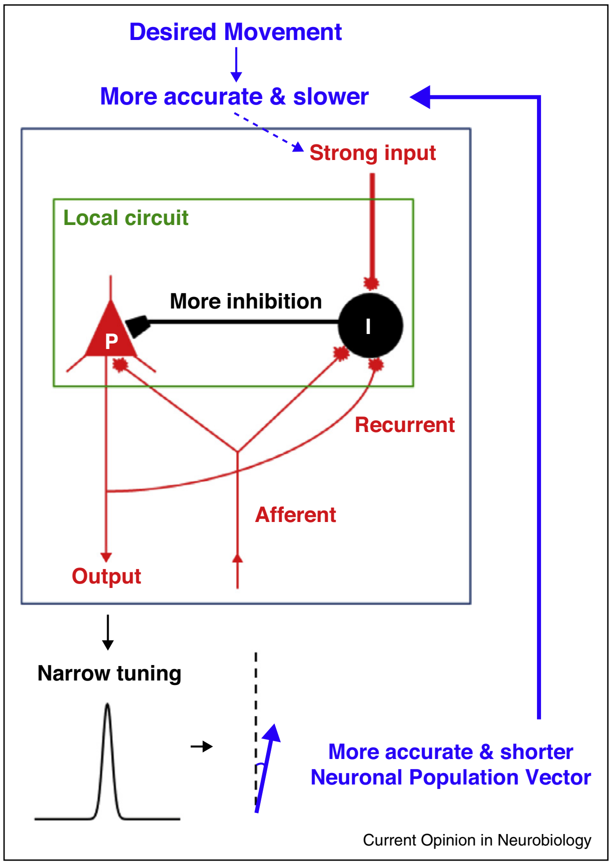
On a systems neural level, the overall findings above likely reflect the rich interconnectivity and large convergence in the motor cortex. Early anatomical work indicated dense connectivity within a 0.2–0.3 mm radius, and a sparser one extending up to 2–3 mm [34]. Cortico-cortical projections to the motor cortex are also substantial [35,36]. Substantial convergence from various thalamic loci has been demonstrated [37]. Given that the thalamus is a relay for basal ganglia and cerebellar influences, this convergence attains a special significance as the substrate for modulating motor cortical cell activity in an integrated way by subcortical inputs [5••].

Thus the issue of coding of movement in the motor cortex can be dealt with in two different planes. The first, descriptive plane addresses the direct relations between motor cell activity and parameters of integrated movements. The value of this approach is that it provides a direct link between neural activity and behavior, hence its power in predicting the unfolding movement trajectory with enough lead to guide a prosthetic arm. The second plane concerns explanations within a neural systems framework, namely the modulation of motor cortical cell activity by a variety of neural signals emanating from the periphery or arising from interacting CNS structures [38]. These signals comprise peripheral afferent inputs being generated continuously during movement, recurrent and local circuit inputs [39], and external inputs, namely thalamic, ipsicortical and callosal inputs during movements of the arm and hand. In a larger sense, motor cortex is a crucial node in an extensively distributed movement control network [5••].

With respect to the local circuit mechanisms affecting the coding of movement in the motor cortex, we proposed recently that local inhibitory mechanisms may be intimately involved in controlling the directional accuracy and speed of the reaching movement [5••]. Specifically, we hypothesized that the width of the directional tuning curve could be the key factor governing the directional accuracy of the population vector and its instantaneous length (and, hence, movement speed). This hypothesis was first tested using modeling, as follows [5••]. We varied systematically the width of the directional tuning curve and determined the direction and length of population vectors calculated from sets of tuning curves of different widths. These results of the modeling studies were confirmed by applying the same analyses to experimental data from previous motor cortical recordings [40••]. In addition, it was found from the latter analyses that the rate of cell discharge during a control period (during which the monkey was exerting a constant load) was significantly and positively associated with the width of the tuning curve. This implied, in turn, that this 'resting' discharge rate could specify the directional accuracy and speed of reaching. Since it is very likely that the resting discharge rate would be the outcome of a varying strength of inhibition, it follows that this could be the neural mechanism by which variable inhibitory drive would control coding of key movement parameters. This idea is illustrated for the two cases of more accurate (and slower) vs. less accurate (and faster) movements in Figures 3 and 4, respectively.

Although the role of inhibition in the motor cortex has not yet been extensively studied, its role in shaping tuning in the visual cortex has been actively investigated since the early 1970s [41]. There is currently general agreement that inhibition plays a major role in sharpening the orientation selectivity of V1 cells (see [42] for a review). A general, nonspecific, 'untuned' inhibition is thought to be the local cortical network mechanism by which weak excitation around a focused excitatory drive at the preferred orientation is eliminated, thus resulting in a sharpened orientation selective tuning curve in primate V1 [43]. A connection between inhibition, neuronal activity, orientation tuning and behavior was recently demonstrated using optogenetic intervention in the visual cortex of mice yielded the predicted results [44••]. Specifically, activation of a certain kind of inhibitory interneurons produced reduction of resting discharge rate, sharper orientation tuning curves, and improvement in behavioral discrimination of gradient orientation. In a way, such a role of inhibition in shaping of neuronal properties and behavior is very similar to the role of Renshaw inhibition in the spinal cord in sharpening the locus of motoneuron excitation by eliminating weak excitatory fringe [45] and the effect of recurrent inhibition in the motor cortex in spatial sharpening of the focus of excitation [46,47,48,49]. A systematic and detailed investigation of inhibitory interneuronal mechanisms in the motor cortex remains to be carried out.

Figure 3



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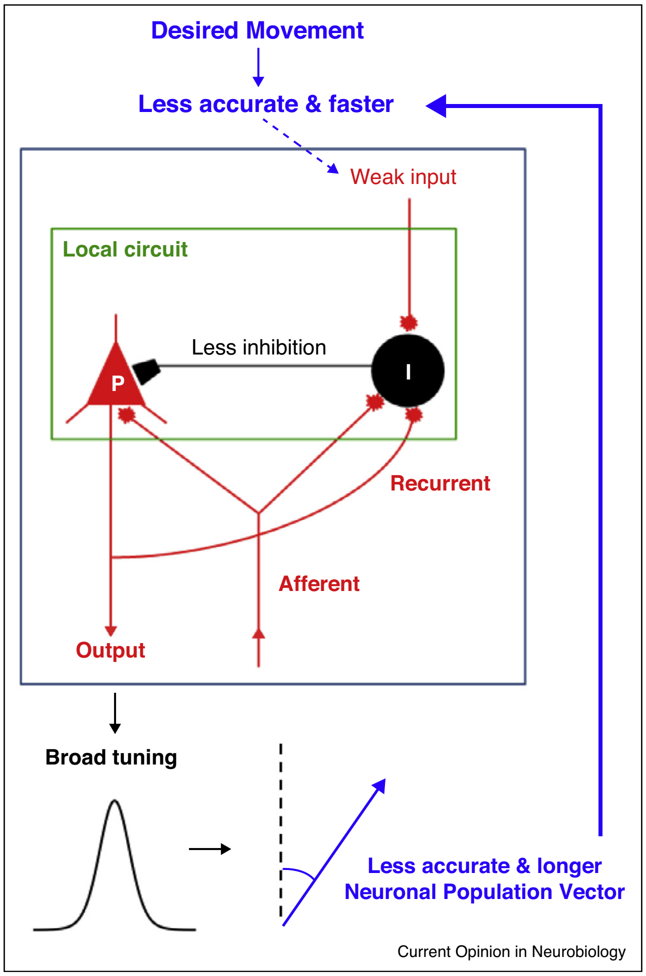
Schematic diagram to illustrate the hypothesis of directional accuracy via a variably tuned inhibitory drive: strong inhibitory drive leads to accurate and slower movement by reducing the directional tuning width and producing an accurate and short population vector. (See text for details.) Red and black terminals indicate excitatory and inhibitory synapses, respectively. P, pyramidal cell; I, inhibitory interneuron.

Figure 4



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Schematic diagram to illustrate the hypothesis of directional accuracy via a variably tuned inhibitory drive: Weak inhibitory drive leads to less accurate and faster movement by increasing the directional tuning width and producing a less accurate and longer population vector. (See text for details.) Conventions as in Figure 3.

Future directions

It is clear that neuroprosthetics is the arena for the ultimate testing of the utility of movement coding schemes in the motor cortex. Unlike pure theory or speculation, neuroprosthetics is the real-world platform where coding schemes can be tested. The fact that the population vector decoding has been very successful in motor cortical prosthetic control [21,22,23,24] is itself evidence for its utility, and the utility of the foundation upon which the calculation of the population vector is based, namely directional tuning of motor cortical cell activity. Further advances in neuroprosthetics may help clarify many open questions in systems neuroscience, including how sensory feedback modifies motor signals, mechanisms of motor skill learning and memory, cognitive motor functions, and the role of oscillatory/synchronous neural activity in neural codes. Finally, manipulating local inhibitory drive might prove a useful and effective tool in improving voluntary control of prosthetic limb movements.

Conflict of interest statement

The authors declare that there is no conflict of interest.

Acknowledgement

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