## CLINICAL IMPLICATIONS OF BASIC RESEARCH

# Turning Thought into Action

Leigh R. Hochberg, M.D., Ph.D.

Patients with spinal cord injury, subcortical stroke, neuromuscular diseases (including amyotrophic lateral sclerosis), and limb amputation have at least two characteristics in common: a brain that wants to direct movement and a body that fails to respond accordingly. Despite intact cortical function, central motor commands in persons with these paralyzing disorders are "disconnected" from their targets, with the neural impulses of intended movement unacknowledged by the downstream central or peripheral nervous system. Pharmacologic, cellular (including stem-cell), and other therapies are designed to repair the injury on-site, but what if the lesion could simply be bypassed, thereby providing a new pathway for these signals to control either one's own limbs or assistive devices such as prosthetic limbs? A recent study by Velliste et al.[1] represents a step toward these goals.
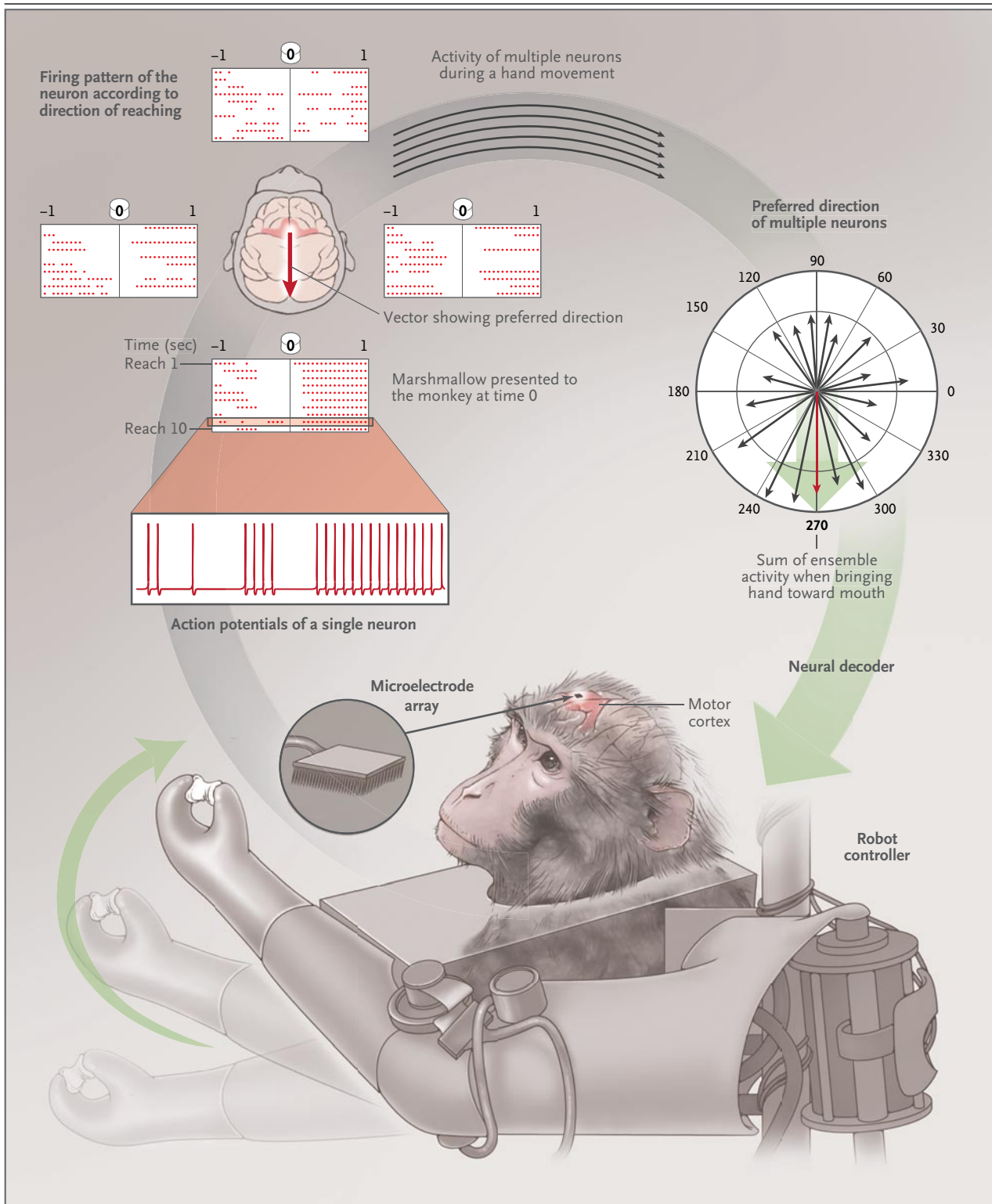
The primary motor cortex (M1) is vital for generating the fine finger and hand dexterity of monkeys and humans. Recordings of single M1 neurons in monkeys performing manual tasks such as gripping a joystick have revealed an association between changes in the action-potential firing rate of these neurons and the dynamics[2] and kinematics of hand movement. In particular, some M1 cells demonstrate "directional tuning": they fire at greatest frequency when an animal reaches in a particular direction (the "preferred direction" for that cell) and at minimum frequency when the animal reaches in the opposite direction (Fig. 1).[3] This can be modeled as a cosine tuning curve by plotting firing rate against direction of movement; knowing a cell's firing rate, one can then predict (with varying degrees of accuracy) the direction of limb movement.

Not much can be gleaned from observation of the instantaneous firing rate of a single neuron, particularly if one wishes to predict the movement of a multijointed limb in three-dimensional space. With recent advances in technology and surgical techniques, however, tiny arrays of microelectrodes can be inserted into the cortex, enabling the recording of activity from a hundred or more neurons in real time. A relatively small ensemble, or population, of directionally tuned M1 neurons allows the location of an animal's hand to be predicted, for example, while the animal moves a joystick to control a cursor in a video game. If the joystick controlling the cursor is then disconnected, that neural output can be decoded into a command signal to move a two- or three-dimensional cursor directly.[4,5] In such experiments, the animal often stops making overt movements of its hand, instead controlling the cursor by "intent" — neural power — alone.

Velliste et al. focused on the neural control of a prosthetic arm for carrying out a task of clear importance — reaching for food, grasping it, and bringing it to the mouth. Two monkeys were trained to use a joystick coupled to a prosthetic arm with shoulder and elbow joints and a terminal gripper. Over 2 to 3 months, control of the prosthetic arm was shifted gradually from joystick to neuron, with neural control driven by a "population vector": the sum of the activity of the simultaneously recorded, directionally tuned M1 neurons. Velliste et al. used cortical activity to define the continually updated end-point location; the robot software then converted this command into the appropriate joint movements. Both monkeys used the robot arm to reach repeatedly for food (such as a marshmallow), grasp it, bring it to the mouth, and release it, all driven solely by the real-time decoding of a small number of motor cortical cells. Moreover, the authors also trained one of the monkeys to open and close the robot gripper using neural activity from this same population of neurons. (For the other animal, the robot gripper opened and closed automatically, depending on the location and movement of the robot arm.)

The monkeys in the study were neurologically intact, but the results are relevant to the development of neural interfaces to help people with paralysis. Our group has previously described a

Firing pattern of the neuron according to direction of reaching

Activity of multiple neurons during a hand movement

Vector showing preferred direction

Time (sec)
Reach 1

Reach 10

Marshmallow presented to the monkey at time 0

Action potentials of a single neuron

Preferred direction of multiple neurons

Sum of ensemble activity when bringing hand toward mouth

Neural decoder

Microelectrode array

Motor cortex

Robot controller

**Figure 1 (facing page). Control of a Robotic Arm by Neural Activity.**

Velliste et al.[1] recently reported an advance in training monkeys to use a robotic arm through impulses generated by the motor cortex. An array of microelectrodes is placed into the motor cortex, enabling the action potentials from dozens of neurons to be recorded simultaneously. If the animal reaches in a specific direction (10 "reaches" down, up, to the right, and to the left are shown), the activity of some neurons will be directionally tuned; the particular neuron shown in this figure is more likely to fire when the animal reaches downward — in this case, after presentation of a marshmallow at time 0. The preferred direction is illustrated by the downward-pointing vector (red arrow). The firing patterns of multiple neurons, which reflect randomly distributed preferred directions, are graphed, with the length of each vector indicative of each neuron's firing rate during movement of the hand. The activity of a population of neurons is fed into a neural decoder. Decoders draw from a variety of established and emerging computational techniques to determine the direction of intended limb movement from the neural population activity and in turn feed that command to a robot controller, which moves the robot arm in the desired direction.

man with tetraplegia from a C4 spinal cord injury who used M1 signals similar to those recorded in the two monkeys to control a computer cursor, a prosthetic hand, and on one occasion, a robot arm for grasping and transporting an object.[6] In this and other cases, the signal extracted from M1 became useful for device control in a matter of minutes. This suggests that the cortical activity associated with intended movement can persist despite paralysis and that this signal could be harnessed for natural reacquisition of one's own limb or to drive an assistive device (such as a wheelchair) or, for amputees, to control a prosthetic limb.

Challenges lie ahead, however, in creating a system that provides around-the-clock, decades-long neural control of implanted or external devices. Most implanted neural-interface systems require a percutaneous connector; fully implantable systems should reduce surgical and postoperative risks and increase the potential of using implanted electrodes in multiple brain regions to provide finer device control. Hardware used to separate and amplify neural signals needs to be miniaturized and automated. Like deep-brain stimulators for movement disorders, these systems should be usable by and beneficial for patients without a caregiver — or a laboratory neurophysiologist — needing to set up the equipment every day. Clinical trials for safety and feasibility are necessary, in part to test the efficacy of these devices in the context of different disease processes. That said, the knowledge gained through the work of Velliste et al.[1] and similar preclinical studies not only provides a better understanding of the brain's mechanisms for motor control and cortical plasticity but also provides a platform on which to further develop neuroengineering strategies to improve mobility and independence.

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